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THE DISPOSAL OF TRITIATED FOLIC ACID INJECTED INTRAVENOUSLY IN MAN*

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THE QUANTITATIVE determination of folic acid, its analogues, and its breakdown products is of interest in the investigation of a number of hematological and other disorders. Chemical methods are available for the determination of high concentrations of folic acid, but at physiological blood and tissue levels, microbiological assay methods are at present widely employed. Much knowledge regarding the metabolism of folic acid has been gained from the application of such methods, but they suffer from several disadvantages, such as the occasional development of mutations of the test organism, inhibition of growth in the presence of samples containing antibiotics or folic acid antagonists, or contamination of the test medium with folic acid active substances or with other bacteria.[1] The circumvention of these and other difficulties requires considerable specialized skill and training on the part of the investigator and his assistants.

It was felt therefore that a simpler assay method might be of value, particularly for absorption and excretion studies in a clinical setting. Such studies have been carried out with Co^{58}-labelled vitamin B_{12} and Co^{60}-labelled vitamin B_{12} by a number of investigators, and with the recent development of satisfactory methods for the routine assay of tritium, analogous studies with tritium-labelled folic acid have now become technically feasible.

Several methods have been utilized for the investigation of the metabolism of folic acid in hematological and other disorders. Among these, the plasma disappearance curve seemed suitable for the initial application of tritium-labelled folic acid. The plasma disappearance curve after a standard dose of folic acid has been intensively investigated by Chanarin and his associates[2-4] by microbiological assay methods and has been shown to be abnormally steep in folic acid deficiency states and also in pernicious anemia.

METHODS

Five hundred milligrams of finely powdered folic acid (U.S.P. grade) was exposed to 15 curies of tritium at 0.39 atms. for 10 days at 27°C. The crude material was precipitated twice at pH 3, and then purified by chromatography on a DEAE-cellulose column pre-equilibrated with 0.01M phosphate buffer at pH 6.9. Most of the impurities were removed by developing with the same buffer, and the remainder of the impurities and pure folic acid eluted separately by raising the buffer strength to 0.2M. Repeated chromatography led to no change in specific activity, which amounted to 12.2 ± 0.2 μc./mg. (mean ± SE). Microbiological assay with *L. casei* (kindly carried out by Dr. B. Cooper) showed a biological activity equal to that of non-irradiated folic acid. Reductive fission and acid hydrolysis showed that 53% of the radioactivity was in the glutamic acid moiety, 26% in the p-aminobenzoic acid moiety, and 21% attached to carbon 9. Folic acid was isolated from the plasma by the addition of known amounts of carrier folic acid and fractional precipitation of the plasma proteins with acetone. On addition of one volume of acetone, most of the proteins were precipitated. On adding a further five volumes of acetone to the supernatant, the folic acid was precipitated with the small residual amount of plasma proteins. The precipitate was redissolved in 0.01M phosphate buffer and chromatographed. Urine after dilution was applied directly to the chromatography column. In this method folic acid was completely separated from folinic acid. After reductive fission to minimize quenching, tritium activity was measured in a Packard TriCarb Liquid Scintillation Spectrometer. All samples were recounted after addition of internal standard. Full details of these methods will be published elsewhere.

RESULTS

After intravenous injection of 15 μg./kg. (8-15 μc.), tritiated folic acid disappears rapidly from the plasma, so that in a typical experiment only 4.0% of the dose per litre of plasma remains at 15 minutes, only 1.1% per litre at one hour, and only 0.1% per litre at six hours (Fig. 1). Measure-

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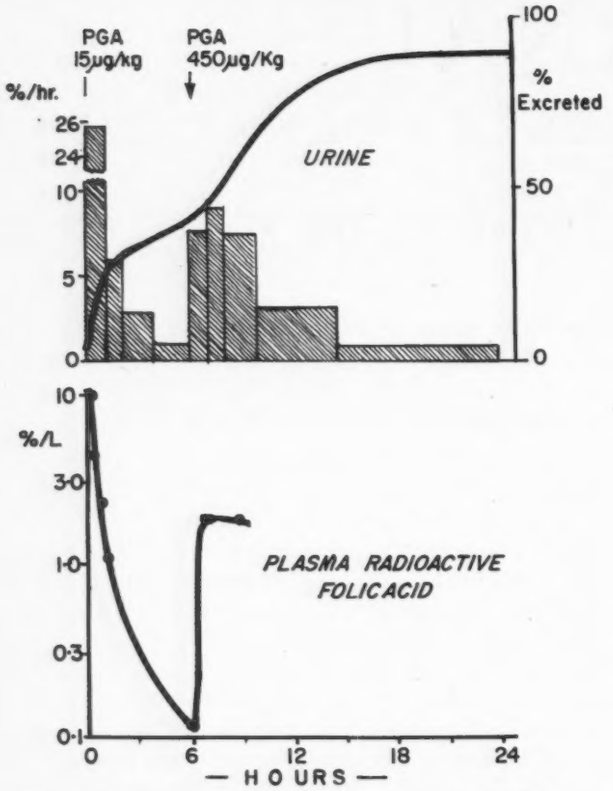

Fig. 1.—Normal man injected with 15 µg./kg. (15.2 µc.) tritiated folic acid intravenously. Six hours after injection of radioactive folic acid a carrier dose of 450 µg./kg. of non-radioactive folic acid was injected intravenously.
Upper graph: *Histogram*: % injected radioactivity excreted per hour in the urine.
Line: Cumulative recovery of injected radioactivity in the urine.
Lower graph: % injected radioactivity recovered per litre of plasma as folic acid.

ment of total radioactivity of the plasma showed that, up to one hour, at least 95% was accounted for by folic acid.

In experiments on six normal subjects, radioactivity equivalent to 28.0 ± 3.5% of the dose was excreted in the urine by the end of six hours, and of this 52.3% was identified as folic acid. In the succeeding 18 hours only a further 1.9 ± 0.1% was excreted, making a total of 29.9% excreted in the first 24 hours. The left-hand portion of Fig. 1 shows plasma concentration and urinary excretion over the first six hours after intravenous injection of folic acid in a typical case.

Thus, in normal subjects 70% of injected radioactivity was still retained at the end of 24 hours, yet the plasma concentration of folic acid was so low that less than 1% of the administered dose was still present in the combined plasma and extracellular spaces, the remainder of the folic acid having apparently entered the intracellular space. It seemed possible that if the intracellular storage were in the form of unchanged folic acid, it might be possible to displace it back into the circulation by administration of a large dose of unlabelled folic acid. The right-hand part of Fig. 1 shows the results of the administration of such a carrier dose. Six hours after injection of 15 µg./kg. of labelled folic acid, the blood level was 0.13% of the dose per litre; within 30 minutes of intravenous injection of 450 µg./kg. of unlabelled folic acid, the blood level of tritiated folic acid had risen to 2% of the dose per litre. Simultaneously, the urinary excretion of radioactivity, which had fallen to less than 1% of the dose per hour, rose and reached a maximum of 9% per hour. This increase in excretion of radioactivity led to the collection of 90.1% of the dose in the first 24 hours compared with 30% when the flushing dose was not given. Of radioactivity excreted after the flushing dose, 65.2% was isolated as folic acid.

While it was found that if the carrier dose were given within six hours, at least 90% of injected radioactivity could be recovered in the urine, this fell in a typical series of experiments to 68.5% if the interval were 24 hours, and to 47.2% if the interval were 72 hours. In each case the same percentage of activity was recovered as folic acid. It was found that pteroyltriglutamate (30 mg.) was as effective as folic acid in flushing out activity but that p-aminobenzoylglutamate (15 mg.) and vitamin B_{12} (1 mg.) were without effect. Amethopterin (7.5 mg. intravenously) had a small flushing effect.

DISCUSSION

The plasma disappearance curve of tritiated folic acid in normal subjects corresponds closely to that obtained by Chanarin *et al.*[2] using unlabelled folic acid and a microbiological estimation method. Tritiated folic acid disappears very rapidly from the blood; the fact that it can be displaced by large doses of carrier shows that it is not broken down but is stored in the cells unchanged. There is no definite evidence as to where this storage occurs, but the results of tissue folic acid estimations[5] suggest the liver, kidneys and bone marrow as important sites.

The decreasing amounts of folic acid displaceable by carrier after 24 hours can be explained either by conversion of the intracellular stores to a non-displaceable form, perhaps a polyglutamate, or alternatively by redistribution of the retained folic acid into cells from which it cannot be displaced. The present data allow no definitive conclusions as to the size of the folic acid pool into which the intravenously administered material disappears, except that it contains at least 60 times as much folic acid as is present in the combined plasma and extravascular spaces. Accepting a normal plasma concentration of approximately 10 µg./l., the extracellular folic acid amounts to about 55 µg. after allowance is made for protein binding; the intracellular pool must therefore be at least 3 mg. of free folic acid.

The flushing effect obtained with pteroyltriglutamate is explainable by the fact that this compound is rapidly hydrolyzed to pteroylglutamate by plasma enzymes.[6] The failure of p-aminobenzoylglutamate to enter the cells (unpublished data) or to flush, and as well the failure of amethopterin to enter the cells nearly as rapidly as folic

acid,[7] suggests a high degree of specificity for transport of folic acid into cells. Likewise the poor flushing effect of amethopterin is probably due to its failure to penetrate the cells rapidly.

A study of the behaviour of tritiated folic acid in disease states is now in progress.

SUMMARY

Tritium-labelled folic acid has been prepared and injected intravenously in man. It disappears very rapidly from the blood and extracellular fluid, but since only 30% of the dose is lost in the urine in six hours, the remainder must have entered intracellular sites. It can be displaced from the cells by nonradioactive folic acid and is recovered in the urine.

REFERENCES

1. GIRDWOOD, R. H.: *Advances in Clin. Chem.*, 3: 235, 1960.
2. CHANARIN, I., MOLLIN, D. L. AND ANDERSON, B. B.: *Brit. J. Haemat.*, 4: 435, 1958.
3. *Idem*: *Proc. Roy. Soc. Med.*, 51: 757, 1958.
4. CHANARIN, I. *et al.*: *Lancet*, 2: 634, 1959.
5. DIETRICH, L. S. *et al.*: *J. Biol. Chem.*, 194: 549, 1952.
6. SCHWEIGERT, B. S.: *J. Lab. & Clin. Med.*, 33: 1271, 1948.
7. FREEMAN, M. V.: *J. Pharmacol.*, 122: 154, 1958.

AN EVALUATION OF THE COBALT-60 VITAMIN B_{12} ABSORPTION TEST*

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SINCE VITAMIN B_{12} was successfully labelled with radioactive cobalt, much has been learned of its metabolism. In addition to the research use of the labelled vitamin, it has proved of value in the diagnosis of vitamin B_{12} deficiency in man, particularly in pernicious anemia. Different methods have been used for measuring the absorption of vitamin B_{12} labelled with cobalt-60 (Co^{60}), but the one most widely employed was described by Schilling in 1953[1] and is sometimes called the Schilling test. He found that when a large parenteral injection of non-radioactive vitamin B_{12} was given one to three hours after the ingestion of a tracer dose of the radioactive vitamin, some of the radioactive vitamin B_{12} was excreted in the urine in the next 24 hours, the amount being proportional to the amount that was absorbed from the gut. With this test, therefore, the renal excretion of vitamin B_{12} labelled with Co^{60} was taken as a measure of vitamin B_{12} absorption. As the intrinsic factor produced in the stomach is normally required for the absorption of vitamin B_{12} given in physiological doses, a person who lacks this factor will show extremely poor absorption of the vitamin, with resulting very low values of excretion of radioactivity in the urine.[2]

The Schilling test has been in use at the University of Alberta Hospital since early in 1956 and during this time has been performed on more than 200 persons. This study is a review of the results of the first 150 tests in an attempt to assess the value of the procedure in the diagnosis of disordered vitamin B_{12} metabolism.

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MATERIALS AND METHODS

Radioactive vitamin B_{12} was obtained from Abbott Laboratories as "Racobalamin capsules". Each capsule contained approximately 0.5 to 0.7 μg. of vitamin B_{12} labelled with approximately 0.5 μc. of Co^{60}. Intrinsic factor concentrate was obtained from desiccated hogs' stomach and supplied from Abbott Laboratories in 30-mg. doses.

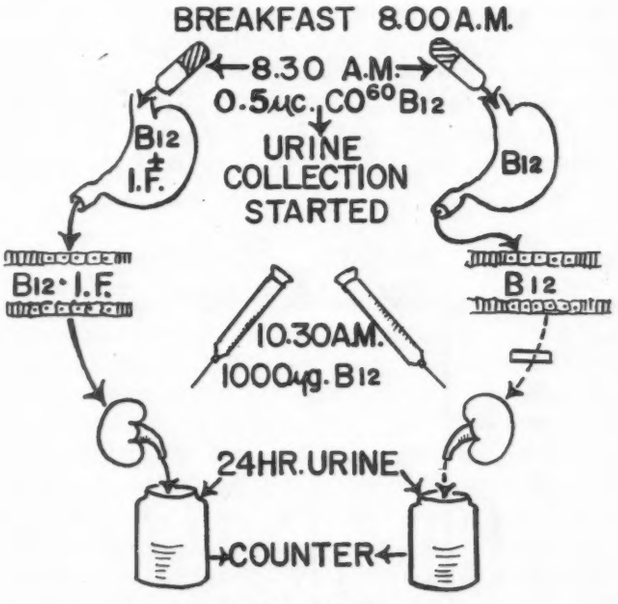

Fig. 1.—The Schilling test.

The test was essentially the same as that described by Schilling (Fig. 1). The patient was given a light breakfast, after which he ingested one capsule containing 0.5 μc. of Co^{60}-labelled vitamin B_{12}. At the same time he voided and discarded that urine specimen. Thereafter, all urine for the next 24 hours was collected in clean jars which had not been previously used for urine collections of radioactive material. Two hours after taking the capsule he was given an intramuscular injection of 1000 μg. of non-radioactive vitamin B_{12}. The pooled urine was adjusted to a volume of 1000 c.c. by the addition of distilled water or the discarding of an

appropriate volume of the mixed specimen. This aliquot was counted directly by placing the specimen in front of a two-inch thallium-activated sodium iodide scintillation crystal. With each new batch of radioactive cobalt, standards were made up to represent 5, 10 and 20% of the administered oral dose in the volume of 1000 c.c. The standards were counted and a standard graph was made with each individual test. The percent radioactivity in the urine specimen was obtained directly from the graph and appropriate corrections made for the initial 24-hour urine volume. When the tests were repeated with intrinsic factor the same procedure was used except that a 30-mg. capsule of intrinsic factor concentrate was given orally along with the capsule of labelled vitamin B_{12}.

RESULTS

This review includes 150 of the first 152 consecutive tests done. Two cases could not be included, because there was felt to be insufficient clinical information available to allow any classification. In addition to the series of 150, the test was performed on 10 males, aged 28 to 80 years, who were known to be free from anemia, gastrointestinal, renal or nervous system disease (Fig. 2).

The results of the Schilling test in these normal controls were all greater than 8.6% excretion. The test was repeated on six of the controls after a check revealed no further radioactivity in the urine. There was considerable variation between duplicate tests on the same individual but the values were all above 8.6%. Intrinsic factor was not given to any of these.

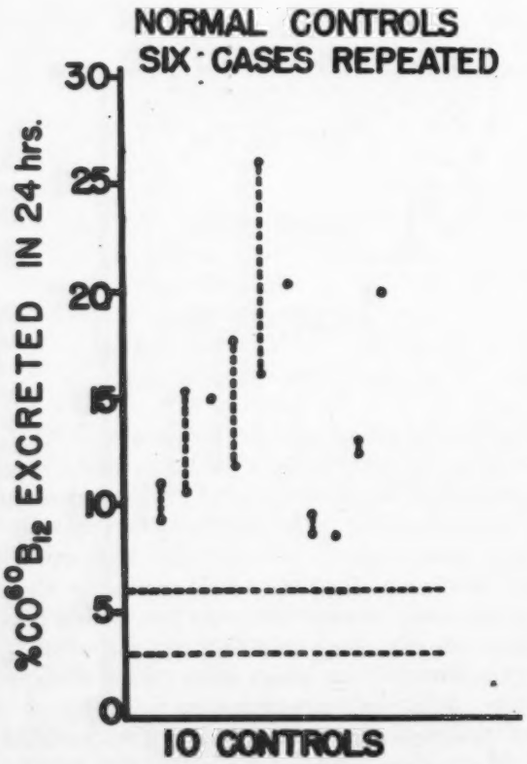

Fig. 2.—Points connected with dotted line indicate tests repeated with intrinsic factor.

The 150 patients tested were grouped as follows: (a) patients recently diagnosed as having pernicious anemia; (b) patients previously diagnosed as having and treated for pernicious anemia; (c) patients with other anemias; (d) patients with predominantly neurological manifestations; (e) patients with malabsorption states; (f) patients with miscellaneous states; (g) patients with a doubtful diagnosis.

Patients Recently Diagnosed as Having Pernicious Anemia

This group of 20 new patients were all diagnosed as having pernicious anemia on such criteria as history, physical findings, peripheral blood smear, bone marrow biopsy, histamine-fast achlorhydria, and reticulocyte response to therapy (Fig. 3). Anemia was present at the time of the test in 19 of the patients and there were neurological abnormalities in 7. Histamine-fast achlorhydria was present in 6, and achlorhydria not tested with histamine in 6 others. No gastric analysis was performed on 8. A bone marrow biopsy was performed in each of 19 patients, and in 17 of these there was a megaloblastic marrow. Of the two remaining patients, one presented with signs of subacute combined degeneration of the spinal cord and was slightly anemic. His bone marrow showed normoblastic hyperplasia. The other had been mildly anemic until just before his admission to hospital when, because of a severe bout of melena, he had been given 1000 c.c. of blood. His bone marrow at the time of examination was normoblastic. In four patients the absorption test was repeated with intrinsic factor, all four showing improved absorption with 24-hour excretion values well within the normal range. The highest value here without intrinsic factor was 2.3%.

Patients Previously Diagnosed as Having and Treated for Pernicious Anemia

On the second scattergraph (Fig. 3) 31 cases previously diagnosed as pernicious anemia are indicated, in 17 of which urinary excretions were greater than 6% and in 14 the values were 2.3% or less. Of the second group (Fig. 3, low absorption) 11 had been receiving liver extract or vitamin B_{12} for years and were being treated at the time of the test. Three had had pernicious anemia diagnosed previously but had been treated only intermittently. Histamine-fast achlorhydria was known to exist in six patients, and there was presumptive evidence of achlorhydria in two more. The test was repeated with intrinsic factor on three patients, with improvement in absorption to within the normal range. Bone marrow biopsies were performed on five of this group of 15 patients, two at the time of the Schilling test, and three at the time of the original diagnosis. All had a megaloblastic bone marrow. The two patients whose bone marrow was examined at the time of the test had not

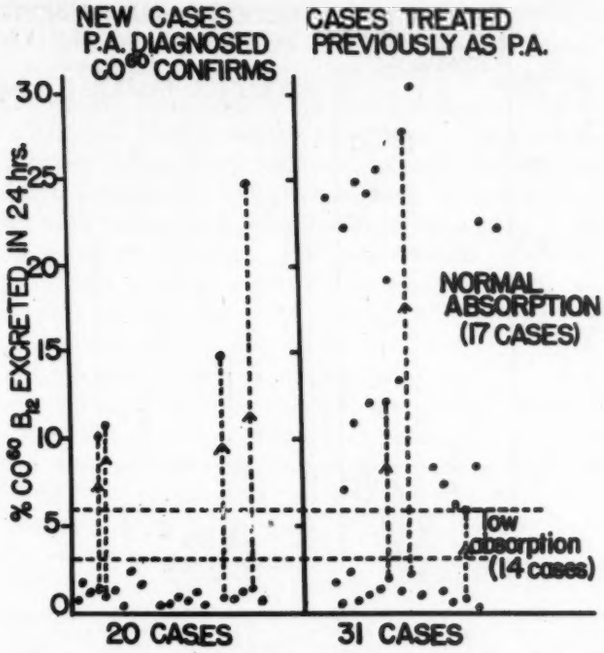

Fig. 3.—On the left are the excretion values in 20 cases where a diagnosis of pernicious anemia had recently been made. The results of repeat absorption with intrinsic factor are indicated by vertical dotted lines.

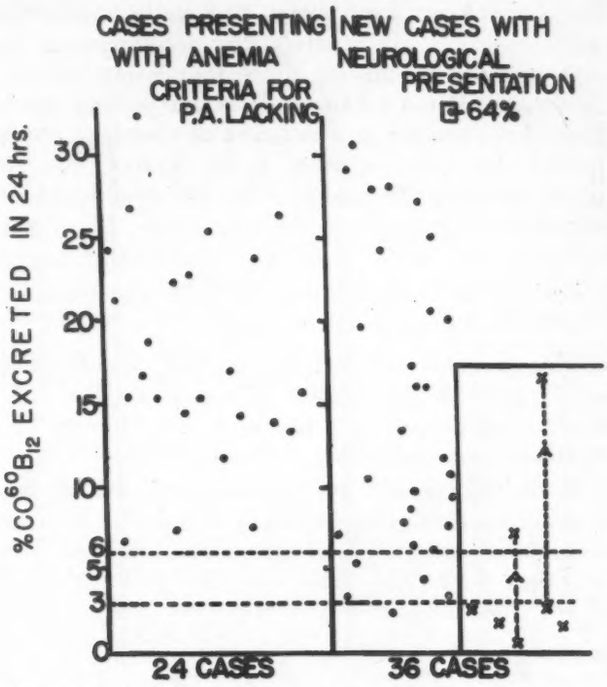

Fig. 4.—The diagnosis in each of the five cases indicated by an X is considered to be subacute combined degeneration of the spinal cord.

received treatment for at least three years. One of these was anemic and the other had a normal hemoglobin value. We have concluded that these patients had pernicious anemia.

Of the individuals with values greater than 6% (Fig. 3, normal absorption) all had been treated by vitamin B_{12} or liver extract previously and seven were known to be receiving treatment at the time of the uptake test. Five had not had vitamin B_{12} for one to two years. Three had free acid in the gastric juice. Only two bone marrow biopsies were performed in this group of 17 and neither was megaloblastic. It may be concluded that none of these patients had pernicious anemia.

In the entire group of 31 cases, the criteria used in the original diagnosis of pernicious anemia are unknown to us.

Patients with Other Anemias (Fig. 4)

A large group comprising 24 patients presented with anemia, except for one who had a normal hemoglobin value, histamine-fast achlorhydria, and a history of refractory anemia previously. All of this group had a urinary excretion above 6.8%. Ten persons had anemia caused by chronic blood loss, eight having bled from the gastrointestinal tract and two from the uterus. Malignant tumour was the cause of bleeding in four of the ten. The causes in the rest of the group were represented by a variety of anemias. Bone marrow biopsies were performed on 13 patients, and all were normoblastic but one, a megaloblastic anemia of pregnancy.

One man aged 57 was diagnosed as having pernicious anemia on the basis of history and physical findings supported by gastric achlorhydria and a megaloblastic bone marrow. A reticulocyte response to liver extract was obtained. Five years later he became anemic again despite vitamin B_{12} therapy, and an enlarging spleen was noted. At age 64 he was diagnosed as having agnogenic myeloid metaplasia, and a Co^{60}-labelled vitamin B_{12} absorption test performed for the first time gave a value of 6.3%. At autopsy the diagnosis of agnogenic myeloid metaplasia was confirmed.

Patients with Predominantly Neurological Manifestations (Fig. 4)

All of this group presented with signs and symptoms predominantly neurological. Twenty-six had an excretion greater than 6%, and of these seven had marked peripheral neuropathy and ten had primary cord lesions. In five patients the clinical and laboratory investigations pointed strongly to subacute combined degeneration of the spinal cord (X, Fig. 4). In all of these, neurological signs predominated and all had values of 2.5% or less. Addition of intrinsic factor in two of these patients increased the excretion value to above 6%. One other improved markedly on vitamin B_{12} therapy. Three of these people had histamine-fast achlorhydria and one was achlorhydric without histamine. No gastric analysis was performed on the fifth. None of them was anemic at the time of the test. These five were considered to have subacute combined degeneration of the cord.

One patient with an excretion of 2.5% may have had pernicious anemia but we had insufficient criteria to make this diagnosis, especially as his test was not repeated with intrinsic factor. Four patients who were not anemic presented with neurological signs and symptoms and had values between 3.3 and 5.3%. Three of these were achlor-

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hydric but none were shown to have histamine-fast achlorhydria. Unfortunately, the Schilling test was not repeated on any of these four using intrinsic factor. Mention must be made of one patient whose absorption was 64%. After careful checking of the results this value appears to be correct, and we could discover no reason why he should not be included.

Patients with Malabsorption from the Bowel (Fig. 5—left-hand scattergraph)

Nine patients are included in this classification, which can be subdivided into two groups: (1) mechanical defects as a result of surgery, and (2) malabsorption syndrome with steatorrhea.

In the first group are two women who after a series of operations on the small bowel, one because of regional enteritis and one after intestinal obstruction, had only nine and ten feet of small bowel remaining, the part removed being mostly ileum in each instance. Their excretions were 0.5 and 0.3%, presumably owing to the absence of the segment of gut where the absorption of vitamin B_{12} actually takes place.[3] One test, when repeated with intrinsic factor, showed no increase.

In the second group (Fig. 5) there were two well-documented cases of non-tropical sprue in young women. One other case was in a middle-aged woman who had a long history of intestinal malabsorption, and who subsequently died with bilateral pyelonephritis and subacute hepatic necrosis. Her absorption value was 13.5%. Six of the group had absorptions repeated with intrinsic factor, and only one, an elderly man who had had a subtotal gastrectomy in 1955 for carcinoma of the stomach, showed an absorption value in the range above 6%. Four of the six had no significant change in absorption after administration of intrinsic factor.

Patients with Miscellaneous Diagnoses (Fig. 5)

There were 13 patients with miscellaneous diagnoses, all with excretions over 6%. None were anemic and none presented with neurological signs or symptoms. Only one had achlorhydria. The reasons for the tests in several of these people were unknown to us.

Patients with a Doubtful Prognosis (Fig. 5)

There were 17 cases in this group with values below 6%. Four of them had an elevated blood urea nitrogen value at the time of the test (x, in circle, Fig. 5). Three of the four subsequently came to autopsy and the autopsy findings suggested that one may have had pernicious anemia. Two of those who underwent autopsy had bilateral chronic pyelonephritis and one had advanced nephrosclerosis. Three patients with low values had been diagnosed clinically as having steatorrhea but in each proper criteria for this diagnosis were lacking. They are

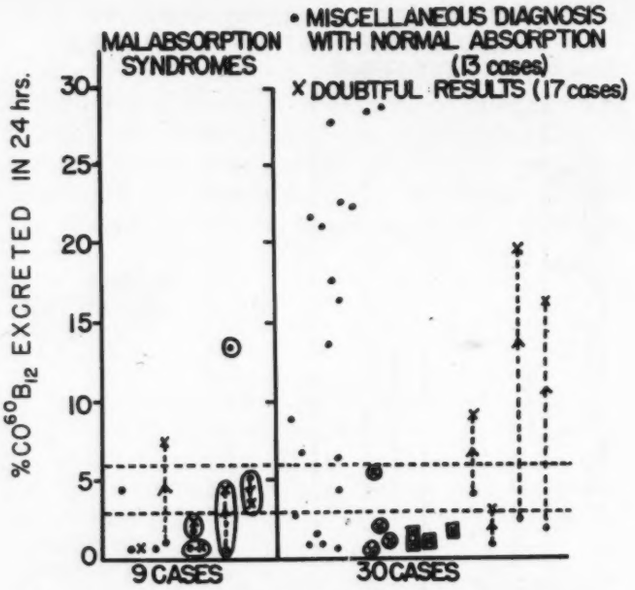

Fig. 5.—On the left graph, the circled dots represent cases of malabsorption syndrome of non-surgical origin. On the right side, the 17 doubtful results are variously represented below the 6% line. X in circle represents a case with an elevated blood urea nitrogen value. X in square represents a doubtful case of steatorrhea.

therefore put in the doubtful classification. On two individuals we had insufficient information to classify them as having pernicious anemia, although their initial absorptions were 2.5% and 0.2% and each showed a marked increase after administration of intrinsic factor. One 57-year-old woman with hypertensive and arteriosclerotic heart disease and a normal hemoglobin value had a value of 4.2%. We were unable to repeat the test either with or without intrinsic factor and she is therefore placed in the doubtful category. Administration of intrinsic factor brought the value in one other case into the normal range but clinically there was considerable doubt that this patient had pernicious anemia. A 78-year-old woman who had been diagnosed as having pernicious anemia at the age of 63 and who had been treated by liver extract ever since, had an uptake value of 0.8%, but also showed free acid in her stomach by tubeless gastric analysis.

DISCUSSION

Vitamin B_{12}, a red crystalline organic compound isolated first in 1948, is the only biological substance known to contain cobalt. Bioassay methods have established that between one and five micrograms are ingested daily.[4] Intrinsic factor, a substance produced normally by the glands of the stomach in man and thought to be a mucopolysaccharide, is necessary for the adequate physiological absorption of vitamin B_{12}. It is thought that intrinsic factor binds vitamin B_{12} in some manner and releases it later for absorption by the mucosa of the lower ileum; the absorption mechanism is as yet unknown. It has been known for some time that in the absence of intrinsic factor, as in pernicious anemia, vitamin B_{12} that has been ingested in physiological amounts is not absorbed.

In the plasma after its absorption, a portion of the vitamin is carried in bound form by the alpha globulins, and the rest is in free form. In this latter state it can be excreted by the kidneys.

Deficient absorption of vitamin B_{12} may occur clinically because of lack of intrinsic factor, lack or dysfunction of absorptive surface, or the binding and utilization of B_{12} by bacteria or parasites before it can be absorbed. The patient with pernicious anemia in relapse exemplifies the failure of absorption of vitamin B_{12} through the absence of intrinsic factor. In our series we have found that such persons have Schilling tests in the range of 2.5% or less, and that this holds true for those who have been diagnosed by accepted criteria, and treated. The addition of intrinsic factor to treated or untreated patients with pernicious anemia results in an absorption in the range above 6%. A diagnosis of pernicious anemia had previously been made on 31 people in our series, 18 of whom were under treatment at the time of the test. Only 14 of the 31 showed absorption values of 2.5% or less and the rest ranged greater than 6%. We believe, therefore, that one of the important uses of the method lies in differentiating true pernicious anemia patients from those who are not but who have been treated as having pernicious anemia, sometimes for years.

Schilling,[5] Klayman and Brandborg[6] and Best *et al.*[7] found values in pernicious anemia patients to be 2.3% or less. Their range for 24-hour urine excretion of Co^{60}-labelled vitamin B_{12} in normal subjects was from 7% to 21%, while values up to 40% for normal individuals and as high as 4.4% for pernicious anemia patients have been published.[8]

In chosen normal individuals and in subjects who have anemias other than pernicious anemia the absorptions were consistently above 6%. Some advantage may therefore derive from the use of the method in solving problems in the diagnosis of anemia. It would appear also from our data that the test has found an increasing use in the differentiation of subacute combined degeneration of the spinal cord from other neurological conditions. Four subjects in our series were considered to have the former diagnosis at a time when anemia had not yet occurred.

A notable fact concerning our group of malabsorption states is that where low values were repeated with intrinsic factor, only one increased to the normal range and that was in a man with carcinoma of the stomach, in which lack of intrinsic factor production appears probable. A low value in malabsorption states was a finding in all but one.

It has been shown by Dunn, Walsh and Holthaus,[9] and others, that renal impairment slows the urinary excretion of vitamin B_{12} in the first 24 hours but if urine collection is extended to 48 hours or longer, normal absorption occurs. It is therefore necessary to know whether renal function is normal in assessing low test values.

SUMMARY

A consecutive series of 150 Co^{60}-labelled vitamin B_{12} absorption tests performed at the University of Alberta Hospital has been reviewed.

Normal individuals and subjects who had an anemia other than pernicious anemia excreted more than 6% of the oral dose in 24 hours.

In pernicious anemia the excretion of Co^{60}-labelled vitamin B_{12} was 2.5% or less. The addition of intrinsic factor increased these values to 6% or higher.

The test probably has its most important use in differentiating patients with true pernicious anemia from those who have had an incorrect diagnosis of pernicious anemia and are being or have been treated for this condition.

The test has found an increasing use in the differentiation of subacute combined degeneration of the spinal cord from other neurological conditions.

Patients with malabsorption states generally have absorption values below 6% but by no means consistently. Addition of intrinsic factor does not increase the absorption.

Our results bear out the contention of Dunn and co-workers that where renal impairment exists, as evidenced by elevated blood urea nitrogen, low Co^{60}-labelled vitamin B_{12} absorption values are found in 24-hour urine collections.

REFERENCES

1. SCHILLING, R. F.: *J. Lab. & Clin. Med.*, **42**: 860, 1953.
2. MOLLIN, D. L.: *Brit. M. Bull.*, **15**: 8, 1959.
3. BOOTH, C. C. AND MOLLIN, D. L.: *Lancet*, **1**: 18, 1959.
4. ESTREN, S., BRODY, E. A. AND WASSERMAN, L. R.: *Advances Int. Med.*, **9**: 11, 1958.
5. SCHILLING, R. F.: *Am. J. Clin. Nutrition*, **3**: 45, 1955.
6. KLAYMAN, M. I. AND BRANDBORG, L.: *New England J. Med.*, **253**: 808, 1955.
7. BEST, W. R. *et al.*: *J. Lab. & Clin. Med.*, **44**: 767, 1954 (abstract).
8. SCHWARTZ, M., LOUS, P. AND MEULENGRACHT, E.: *Lancet*, **2**: 1200, 1958.
9. DUNN, A. L., WALSH, J. R. AND HOLTHAUS, J. M.: *A.M.A. Arch. Int. Med.*, **101**: 927, 1958.

The nation-wide program of hospital insurance, operating in nine provinces at the end of the year 1959, has radically altered the traditional methods of financing hospital care. It has employed the grant-in-aid technique to achieve decentralization in federal-provincial relations within a federal state and to strengthen the traditional pattern of community hospital services within each province. Final cost data on the program are not yet available. However, federal advance payments from July 1, 1958, to December 31, 1959, totalled $164,552,000; the estimated [federal] cost for the 1960-61 fiscal year was $167 million. The estimated total population coverage in the nine participating provinces at the end of the year 1959 was about 12 million persons, or nearly 95% of the combined population of these provinces.—*Hospital Care in Canada* (Health Care Series, Memorandum No. 12, Department of National Health and Welfare), March 1960.

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RADIOACTIVE IODINE IN THE TREATMENT OF HYPERTHYROIDISM

EXPERIENCE AT THE TORONTO GENERAL HOSPITAL, 1950-58*

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PART III‡

POSSIBLE BIOLOGICAL HAZARDS FROM RADIOACTIVE IODINE THERAPY

RADIATION AT any level cannot be considered harmless; in view of the prevailing lack of definitive knowledge of the dangers, and the controversial nature of this subject, it is impossible to be dogmatic regarding the possible hazards implicit in the therapeutic use of radioactive iodine. An attempt will be made, nevertheless, to summarize our views under the headings below.

(i) *Fertility and genetic effects*

The cure of hyperthyroidism by whatever means is often associated with a return of normal fertility from a state of relative infertility. Thus, after radioactive iodine therapy, there is often a return of normal libido in males, and an increased number of pregnancies in female patients. Twenty of our female patients have become pregnant since treatment, an incidence similar to that in other series. The babies have all been normal. Menstrual disturbances have not been known to result from I^{131} therapy.[1, 26, 59]

It has been concluded by all workers that radioactive iodine therapy in hyperthyroidism has not interfered with the fertility of males or females.

The fear of *genetic effects* from the therapeutic use of radioactive iodine has aroused considerable controversy. From direct measurement of ovarian radiation (post-I^{131}) in autopsy observations,[1, 4, 60, 61] it would appear that there is insufficient ovarian radiation from therapeutic I^{131} to induce mutations. Silver has noted that the total dosage to the ovaries from an average therapeutic dose does not exceed that delivered by diagnostic intestinal roentgen investigations,[3] and to this may be added vertebral films, cystograms and salpingograms.[62] Myant[63] has estimated that a *maximum* of 2.02 rep per millicurie of I^{131} is picked up by the ovaries in hyperthyroid patients. Working from Clark's[64] figures regarding the distribution and utilization of radioactive isotopes in the United States, the British Medical Research Council[65] has calculated that the gonadal radiation in the U.S.A. population derived from radioactive isotopes amounts to almost 9% of the natural background of 95 millirems per year. However, Johns and Taylor,[66] using Canadian distribution figures, have calculated that the dose to the gonads, up to the age of 30, from radioisotopes in Canada in 1956 was less than 0.5% of that due to natural background. These studies involve the theoretical distribution of the radiation over the entire population. These same authors, moreover, have calculated the maximum dose to the gonads in hyperthyroid patients, and obtained a figure of 0.45 rads per millicurie dose of I^{131}, a figure quite different from that obtained by Myant. Another observer, Bercy,[96] has stated that 10 mc. of I^{131} will deliver only 1.25 rads to the ovaries. Blomfield *et al.*[26] in Sheffield, England, have calculated that the contribution of I^{131} therapy for hyperthyroidism to the genetically significant dose is approximately 0.3% of the natural background, as compared with the contribution of diagnostic radiology of 22% of the natural background.

Although we obviously cannot have any dogmatic data bearing on actual mutation rates for several generations, it is believed that radioactive iodine as presently utilized in hyperthyroidism will have a negligible genetic effect.

(ii) *Pregnancy and Lactation*

Pregnancy remains a contraindication to radioactive iodine therapy, because of the possible deleterious effects of radiation on the fetus with respect to the whole-body fetal radiation, and fetal thyroid irradiation. The fetal thyroid does not begin to accumulate iodine until the fourth month of pregnancy,[67] although one report suggests that the fetal goitre may concentrate iodine as early as 18 weeks.[68] Inadvertently, pregnant patients have been treated with radioactive iodine without ill effects to the fetus, even when treatment was given after the fourth month.[1, 3, 4, 6, 9] However, these observations should not cause any change in policy with regard to the use of this isotope in pregnancy. Our practice generally is to treat hyperthyroid pregnant patients with antithyroid drugs until the pregnancy is concluded.

I^{131} appears in mother's milk, and thus patients should not be treated with I^{131} while nursing.[70]

(iii) *Carcinogenesis*

Both goitrogens[71] and radioactive iodine,[72] either singly or in combination,[73, 74] have been involved in the production of thyroid cancer *in animals* through the prolonged stimulatory effect of thyrotropic hormone. The dose of radioactive iodine

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utilized in the animals was high, compared with human therapeutic doses. Moreover, these animal tumours can be prevented by the administration of thyroxine, or by hypophysectomy.[75]

In hyperthyroid patients given radioactive iodine since the inception of this agent, there has been only one proved case of thyroid cancer, and this was in a child.[76] In the same series, two other children given I^{131} therapy also developed thyroid nodules five years or more after therapy.

Aside from these cases, which have been solely in children, there have been no case reports of carcinoma of the thyroid resulting from I^{131} therapy for hyperthyroidism. This is rather surprising in view of the reported incidence of carcinoma of the thyroid found at operation in patients with hyperthyroidism at the Mayo Clinic between 1936 and 1946, an incidence which was reported as 0.4%.[77] It can only be wondered what radioactive iodine has done to this small percentage, since they have not appeared clinically after the use of the isotope. As pointed out by Chapman and Maloof,[1] "the incidence of carcinomata that may develop in the thyroid glands of patients treated with radioactive iodine will have to exceed 0.4% to suggest a causal relationship".

Critics have suggested that a 20-year period may be necessary for the production of carcinoma of the thyroid. Although this interval has yet to be reached by any treated patient, it seems curious that a few cases have not been reported "en avance". Evans[78] has pointed out that I^{131} releases 97% of its energy in the thyroid gland in 30 days and is largely excreted in the urine. He stated that to induce carcinogenesis, a low level of radiation should be maintained for a period of years.

It is concluded that the carcinogenetic effect of I^{131} in *adult* patients with hyperthyroidism is likely negligible, although further decades are necessary to confirm this view. Similar doses in children, however, may have a significant carcinogenetic effect.

(iv) *Shortened Life Span*

Since the doses of I^{131} used in hyperthyroidism deliver only a few r of whole-body radiation, it is generally accepted that there will be no resultant shortening of life span.[1]

(v) *Leukemia*

Fourteen cases of leukemia[26, 34, 79-83, 97, 104] have now been reported following the use of radioactive iodine (including our one case). In our patient, signs and symptoms of leukemia were recognized only three months after treatment; no blood smear had been read before treatment. It seems quite probable that this patient might have had leukemia at the time of I^{131} administration. In the case of Sheline and Miller,[34] splenomegaly and a high leukocyte count were noted at the time of I^{131} therapy. The remaining seven reported cases had periods of latency of the order of two years. One such report contained a warning regarding the assumption that the association of leukemia and I^{131} therapy for hyperthyroidism is purely due to chance.[83]

Merliss,[84] commenting on Kennedy's article,[83] has pointed out that 10 mc. of I^{131} will deliver about 7 r of whole-body radiation, a dose similar to that delivered by a series of radiographic studies of the back. He referred to Lewis'[85] figures, which indicate that for each absorbed roentgen of whole-body radiation there may be an increase of two cases of leukemia per 1,000,000 persons per year. With a 7 r dose, the increase may be 14 cases per 1,000,000 per year. Since the natural incidence of leukemia (in the United States) is 68 cases per 1,000,000 per year, the predicted rate for persons subjected to a 7 r dosage will be 82 cases per year. Thus there *may* be a 20% increase in the incidence of leukemia in patients treated with I^{131}.

It is likely that other cases of leukemia have occurred following I^{131} therapy, but have not been reported. Similarly, the total number of persons treated with I^{131} is not known. It may be fairly stated, however, that "there is no great increase in leukemia amongst I^{131}-treated patients". It is considered that the risks of surgical thyroidectomy are greater than those of radioactive iodine.

Merliss further adds that "the increased incidence of leukemia from therapeutic use of I^{131} is no greater than that which theoretically results from a series of x-ray studies of the back, and there are few physicians who would give patients potentially hazardous drugs or ask them to undergo a sizable surgical procedure to avoid the dangers of an x-ray examination of the back".

COMPARISON OF THERAPEUTIC RESULTS WITH THOSE OF THYROIDECTOMY

It is difficult at this stage to compare adequately radioactive iodine therapy with surgical thyroidectomy. Although indications for operation are beyond the scope of this paper, both forms of therapy have their places in the therapeutic armamentarium. The difficulty lies in comparing the aforementioned hypothetical dangers with the real, known hazards of thyroidectomy, and in the comparison of the morbidity from this operation with the morbidity of continuing hyperthyroidism. The operative morbidity rate varies from 0 to 3.1% in different series.[86, 98-101] Recurrent or persistent hyperthyroidism has been noted in 2.4 to 9.6% of postoperative patients, whereas late recurrences are very rare in I^{131}-treated patients. Permanent postoperative hypothyroidism has been reported in 0.2 to 13.9%. These include only obvious cases of hypothyroidism, the mild and subclinical forms generally being unrecognized, while, in general, follow-up periods were not long enough to determine the incidence of late-onset hypothyroidism. In our experience, unsuspected mild hypothyroidism has

been found in an appreciable number of patients years after surgical thyroidectomy.

Adjacent tissues are virtually never damaged by radioactive iodine therapy, although five questionable cases of parathyroid damage have been described.[87-91] Vocal cord paralysis and hypoparathyroidism have each been reported in about 1% of thyroidectomy patients. It is unlikely that the incidence of ocular complications is much different with the two forms of therapy, and the comparative incidence of thyroid storm (rare) is likewise in some doubt. Previous therapy would, of course, influence the latter.

SUMMARY

A review of 542 hyperthyroid patients treated by I^{131} at the Toronto General Hospital between 1950 and 1958 is presented. This group included 403 patients with diffuse hyperplastic goitre and 139 patients with toxic nodular goitre. It has become our practice to treat all non-pregnant hyperthyroid patients over the age of 25 years by this isotope.

The method for assessing the initial dose of I^{131} is described. In general, patients with toxic nodular goitres received much larger doses. Of the "diffuse hyperplastic" group, 72% were cured with one dose, the remainder requiring two or more doses. A greater percentage of the "toxic nodular group" required only one dose. No cases of complete resistance to I^{131} therapy were encountered.

Permanent hypothyroidism was produced in 16.3% of those so treated, but in 6.5% it was very mild. Many of these were detected solely by laboratory procedures. The incidence of *clinical* hypothyroidism (total 9.8%) was much lower in the "toxic nodular group" (3.7%) than in the "diffuse hyperplastic" group (11.8%). There was a continuing incidence of late hypothyroidism, occurring years after therapy; some of these patients had undergone a transient period of hypothyroidism shortly after treatment, then recovered for some years.

Factors possibly related to the response to treatment and to the development of hypothyroidism have been analyzed. Recurrent hyperthyroidism after thyroidectomy was associated with a significant increase in the incidence of post-I^{131} hypothyroidism, while pretreatment with antithyroid drugs seemed to reduce radiosensitivity in the "diffuse" group.

No late recurrences of hyperthyroidism were noted.

Twenty-one deaths occurred within two years of therapy. In most, there was no obvious relation to therapy, while in none was there a clear-cut cause-and-effect relationship to I^{131} therapy. Nevertheless, elderly or very ill patients should be treated only after they have been rendered euthyroid by antithyroid drugs.

Fertility has not been affected by I^{131} therapy, but the use of this isotope in pregnancy is contraindicated because of the possible ill effects on the fetus. The possibility of genetic effects appears to be negligible, as judged by the gonadal radiation doses received in I^{131} therapy. The fear of carcinoma of the thyroid likewise appears to be receding if the therapy is utilized only in adults.

Leukemia has been reported in 14 instances. However, the statistical import is not clear, since the total number of cases of leukemia and of persons treated by I^{131} is not known. It may be that there is a slight increase in the incidence of leukemia following radioactive treatment, comparable to that possibly induced by certain diagnostic radiological procedures, but this is insufficient to warrant any change in policy regarding the use of I^{131}.

After consideration of these hypothetical dangers, it is concluded that the use of radioactive iodine is a safe, effective form of therapy for adult, non-pregnant hyperthyroid patients, and is to be preferred to surgical thyroidectomy.

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REFERENCES

1. CHAPMAN, E. M. AND MALOOF, F.: *Medicine*, **34**: 261, 1955.
2. BEIERWALTES, W. H. *et al.*: Clinical use of radioisotopes, W. B. Saunders Company, Philadelphia, 1957.
3. QUIMBY, E. H., FEITELBERG, S. AND SILVER, S.: Radioactive isotopes in clinical practice, Lea & Febiger, Philadelphia, 1958.
4. WERNER, S. C., ed.: The thyroid, Paul B. Hoeber, Inc., New York, 1955.
5. RALL, J. E.: *Am. J. Med.*, **20**: 719, 1956.
6. POCHIN, E. E.: *In*: Modern trends in endocrinology, edited by H. Gardiner-Hill, Butterworth & Co., Ltd., London, 1958, pp. 46-51.
7. RIGGS, D. S.: *Pharmacol. Rev.*, **4**: 284, 1952.
8. MYANT, N. B. *et al.*: *Clin. Sc.*, **9**: 405, 1950.
9. BERSON, S. A.: *Am. J. Med.*, **20**: 653, 1956.
10. MICHEL, R.: *Ibid.*, **20**: 670, 1956.
11. FERMI, E.: *Nature*, **133**: 757, 1934.
12. HERTZ, S., ROBERTS, A. AND EVANS, R. D.: *Proc. Soc. Exper. Biol. & Med.*, **38**: 510, 1938.
13a. HAMILTON, J. G. AND SOLEY, M. H.: *Am. J. Physiol.*, **127**: 557, 1939.
13b. *Idem*: *Ibid.*, **131**: 135, 1940.
14. HERTZ, S. AND ROBERTS, A.: *J. Clin. Investigation*, **21**: 624, 1942 (abstract).
15. HAMILTON, J. G. AND LAWRENCE, J. H.: *Ibid.*, **21**: 624, 1942.
16. SATTLER, H.: Basedow's disease. English translation by G. W. Marchand and J. F. Marchand, Grune & Stratton, New York, 1952, p. 284.
16a. MURRAY, G. R.: *Trans. Roy. M. & Chir. Soc.*, **86**: 141, 1902.
17. BERMAN, M., BECKER, D. V. AND BENUA, R. S.: *J. Clin. Endocrinol.*, **17**: 1222, 1957.
18. BARKER, S. B., HUMPHREY, M. J. AND SOLEY, M. H.: *J. Clin. Investigation*, **30**: 55, 1951.
19. HUBER, N.: *Canad. J. M. Tech.*, **18**: 77, 1956.
20. WILLIAMS, R. H. *et al.*: *Am. J. Med.*, **7**: 702, 1949.
21. WERNER, S. C.: *M. Clin. North America*, **36**: 623, 1952.
22. WERNER, S. C., QUIMBY, E. H. AND SCHMIDT, C.: *Radiology*, **51**: 564, 1948.
23. *Idem*: *Am. J. Med.*, **7**: 731, 1949.
24. MARINELLI, L. D., QUIMBY, E. H. AND HINE, G. J.: *Am. J. Roentgenol.*, **59**: 260, 1948.
25. LOEVINGER, R.: Calculation of radiation dosage in internal therapy with I^{131}. *In*: Radioisotopes in Medicine September 1953, U.S. Atomic Energy Commission, Washington, D.C., 1955, p. 91.
26. BLOMFIELD, G. W. *et al.*: *Brit. M. J.*, **1**: 63, 1959.
27. FREEDBERG, A. S. *et al.*: *J. Clin. Endocrinol.*, **12**: 86, 1952.
28. SEED, L. AND JAFFE, B.: *Radiology*, **63**: 551, 1954.
29. MILLER, E. R. AND SHELINE, G. E.: *Ibid.*, **57**: 720, 1951.
30. BLOMFIELD, G. W. *et al.*: *Brit. M. J.*, **2**: 373, 1951.
31. COOK, J. R., JONES, R. W. AND MCCULLAGH, E. P.: *J. Clin. Endocrinol.*, **15**: 1512, 1955.
32. CASSIDY, C. E. AND ASTWOOD, E. B.: *New England J. Med.*, **261**: 53, 1959.
33. BARTELS, E. C.: Thyroidectomy for hyperthyroidism following failure to respond to radioiodine therapy. Transactions of the American Goiter Association, April 30-May 2, 1959.
34. SHELINE, G. E. AND MILLER, E. R.: *A.M.A. Arch. Int. Med.*, **103**: 924, 1959.
35. SOLEY, M. H.: *California & West. Med.*, **60**: 64, 1944.
36. JEFFERIES, W. *et al.*: *J. Clin. Endocrinol.*, **16**: 1438, 1956.
37. CLARK, D. E. AND RULE, J. H.: *J. A. M. A.*, **159**: 995, 1955.
38. WERNER, S. C., COELHO, B. AND QUIMBY, E. H.: *Bull. New York Acad. Med.*, **33**: 783, 1957.
39. ALBRIGHT, E. C.: *Wisconsin M. J.*, **52**: 631, 1953.
40. NICHOLSON, W. M., GARRETT, N. H. AND BISHOPRIC, G. A.: *North Carolina M. J.*, **15**: 544, 1954.
41. BALLS, K. F. *et al.*: *Radiology*, **64**: 858, 1955.
42. HAMWI, G. J. AND GOLDBERG, R. F.: *A.M.A. Arch. Int. Med.*, **97**: 453, 1956.
43. MACGREGOR, A. G.: *Brit. M. J.*, **1**: 492, 1957.
44. NADLER, S. B. *et al.*: *J. Louisiana M. Soc.*, **106**: 368, 1954.
45. RINKOFF, S. *et al.*: *New York J. Med.*, **54**: 2470, 1954.
46. BEIERWALTES, W. H. AND JOHNSON, P. C.: *A.M.A. Arch. Int. Med.*, **97**: 393, 1956.
47. MCCULLAGH, E. P.: *Ann. Int. Med.*, **37**: 739, 1952.
48. MILLER, E. R., DAILEY, M. E. AND MCCORKLE, H. J.: *A.M.A. Arch. Surg.*, **65**: 12, 1952.

49. WAYNE, E. J.: *Proc. Roy. Soc. Med.*, **45**: 338, 1952 (abridged).
50. RALL, J. E. *et al.*: *J. Clin. Endocrinol.*, **13**: 1369, 1953.
51. SEED, L. AND JAFFE, B.: *Ibid.*, **13**: 107, 1953.
52. BAUER, F. K. AND BLAHD, W. H.: *A.M.A. Arch. Int. Med.*, **99**: 194, 1957.
53. FEITELBERG, S. *et al.*: *Arch. Int. Med.*, **85**: 471, 1950.
54. NELSON, R. B., CAVENAGH, J. B. AND BERNSTEIN, A.: *Illinois M. J.*, **101**: 265, 1952.
55. HORST, W.: *Deutsche med. Wchnschr.*, **76**: 1052, 1951.
56. BLIZZARD, R. M. *et al.*: *New England J. Med.*, **260**: 112, 1959.
57. BELYAVIN, G. AND TROTTER, W. R.: *Lancet*, **1**: 648, 1959.
58. MALOOF, F.: *Endocrinology*, **56**: 209, 1955.
59. MCCULLAGH, E. P. AND RICHARDS, C. E.: *A.M.A. Arch. Int. Med.*, **87**: 4, 1951.
60. KURLAND, G. S. AND FREEDBERG, A. S.: *J. Clin. Endocrinol.*, **11**: 843, 1951.
61. TRUNNELL, J. B. *et al.*: *Ibid.*, **10**: 1007, 1950.
62. MILLER, J. E. AND SWINDELL, G. E.: *J. A. M. A.*, **170**: 761, 1959.
63. MYANT, N. B.: Treatment of thyrotoxicosis by radioiodine, *In*: Therapeutic use of artificial radioisotopes, edited by Paul F. Hahn, John Wiley & Sons, Inc., New York, 1956.
64. CLARK, S. H.: *Bull. Atomic Scientists*, **12**: 14, 1956.
65. Medical Research Council: The hazards to man of nuclear and allied radiations, Command Paper 9780, Her Majesty's Stationery Office, London, June 1956.
66. JOHNS, H. E. AND TAYLOR, R. M.: Dose from unsealed radio-nuclides, *In*: Report of the United Nations Scientific Committee on the Effects of Atomic Radiation: Canadian Report, U.N. Document Series A/AC. 82/G/R, New York, 1958.
67. CHAPMAN, E. M. *et al.*: *J. Clin. Endocrinol.*, **8**: 717, 1948.
68. GOLDSTEIN, D. J.: *South African M. J.*, **32**: 239, 1958.
69. HODGES, R. E. *et al.*: *J. Clin. Endocrinol.*, **15**: 661, 1955.
70. MILLER, H. AND WEETCH, R. S.: *Lancet*, **2**: 1013, 1955.
71. PURVES, H. D., GRIESBACH, W. E. AND KENNEDY, T. H.: *Brit. J. Cancer*, **5**: 301, 1951.
72. GOLDBERG, R. C. AND CHAIKOFF, I. L.: *A.M.A. Arch. Path.*, **53**: 22, 1952.
73. DONIACH, I.: *Brit. J. Cancer*, **7**: 181, 1953.
74. *Idem*: *Ibid.*, **4**: 223, 1950.
75. MALOOF, F.: *Endocrinology*, **56**: 209, 1955.
76. SHELINE, G. E., LINDSAY, S. AND BELL, H. G.: *J. Clin. Endocrinol.*, **19**: 127, 1959.
77. PEMBERTON, J. DE J. AND BLACK, B. M.: *Trans. Am. Goiter A.*, 163, 1948.
78. EVANS, R. D.: *Acta Unio internat. contra cancrum*, **6**: 1229, 1950.
79. POCHIN, E. E., MYANT, N. B. AND CORBETT, B. D.: *Brit. J. Radiol.*, **29**: 31, 1956.
80. ABBATT, J. D., FARRAN, H. E. A. AND GREENE, R.: *Lancet*, **1**: 782, 1956.
81. Proceedings of the conference on radioiodine, sponsored by the Argonne Cancer Research Hospital, United States Atomic Energy Commission, and the Clinics of the University of Chicago, Chicago, Ill., November 5 and 6, 1956; edited by D. E. Clarke. Office of Technical Services, Department of Commerce, Washington, D.C., 1957.
82. WERNER, S. C. AND QUIMBY, E. H.: *J. A. M. A.*, **165**: 1558, 1957.
83. KENNEDY, W. M. AND FISH, R. G.: *New England J. Med.*, **260**: 76, 1959.
84. MERLISS, R. R.: *Ibid.*, **260**: 562, 1959.
85. LEWIS, E. B.: *Science*, **125**: 965, 1957.
86. BUXTON, O. H. AND WILLCOZ, A.: *Arch. Middlesex Hosp.*, **2**: 98, 1952.
87. TIGHE, W. J.: *J. Clin. Endocrinol.*, **12**: 1220, 1952.
88. BOULET, P., MIROUZE, J. AND RIBSTEIN, M.: *Ann. endocrinol.*, **13**: 801, 1952.
89. KLOTZ, H. P., CAROIT, M. AND LUMBROSO, P.: *Ibid.*, **14**: 838, 1953.
90. LANGERON, L. AND VINCENT, G.: *J. Sci. méd. Lille*, **5**: 135, 1957.
91. GILBERT-DREYFUS, ZARA, M. AND GALI, P.: Semaine hôp., Paris, **34**: 1, 1958.
92. CROOKS, J. *et al.*: *Brit. M. J.*, **1**: 151, 1960.
93. GREEN, N.: *Bull. Med. Staff Meet., New Mt. Sinai Hosp., Toronto*, **2**: 16, 1960.
94. RUBENFELD, S. *et al.*: *A.M.A. Arch. Int. Med.*, **104**: 532, 1959.
95. DONIACH, D., HUDSON, R. V. AND ROITT, I. M.: *Brit. M. J.*, **1**: 365, 1960.
96. BERCY, A.: *Am. J. Roentgenol.*, **79**: 737, 1958 (abstract).
97. POCHIN, E. E.: The occurrence of leukaemia following radioiodine therapy, Transactions, Fourth International Goitre Conference, London, England, July 5-8, 1960. (To be published as Vol. 26 of *Excerpta Medica International Congresses.*)
98. GOLDMAN, L.: *J. Clin. Endocrinol.*, **8**: 781, 1948.
99. PEMBERTON, J. DE J., HAINES, S. F. AND KEATING, F. R., JR.: *Ibid.*, **9**: 1232, 1949.
100. PINTO, A. D.: *Rev. paulista med.*, **38**: 627, 1951.
101. SEED, L.: *S. Clin. North America*, **32**: 155, 1952.
102. ASTWOOD, E. B.: Treatment of hyperthyroidism, *In*: Clinical endocrinology, Vol. I, E. B. Astwood, editor, Grune & Stratton, New York, 1960.
103. CHEITLIN, M. D., BERNSTEIN, R. AND LANGDON, E. A.: *Ann. Int. Med.*, **52**: 349, 1960.
104. BURNS, T. W., VICKERS, R. AND LOWNEY, J. F.: *A.M.A. Arch. Int. Med.*, **106**: 97, 1960.
105. ELLER, M. *et al.*: *Ann. Int. Med.*, **52**: 976, 1960.
106. DE GENNES, J. L., COCOVINIS, C. AND FAUVERT, R.: *Semaine hôp. Paris*, **35**: 1473, 1959.
107. DEGOWIN, E. L. *et al.*: *A.M.A. Arch. Int. Med.*, **104**: 959, 1959.
108. LAMBERG, B. A. *et al.*: *Acta med. scandinav.*, **165**: 245, 1959.

CONTINUOUS EPIDURAL ANALGESIA IN THE TREATMENT OF FROSTBITE
A REPORT OF THREE CASES*

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WHEN A REGION of the body is subjected to cold, the body reacts by reducing the blood supply to that region, thus conserving heat in the entire body at the expense of the affected member. This response, mediated through the autonomic nervous system, is basically arteriolar and capillary vasospasm.

The protective glomus body shunt mechanisms in the periphery of the limbs close to increase blood flow to the tips of the digits. Prolongation of exposure to cold, producing further vasospasm proximally, isolates the part from the further warming effect of the blood, and "frostbite" is established.

The time period of exposure to subnormal body temperatures is important, as the reaction occurs even with exposure at a moderate subnormal temperature for a prolonged period, e.g. immersion foot. This may produce as much tissue necrosis peripherally as short periods of exposure to severe cold.

If the vasospasm is prolonged, retrograde thrombosis of the arterial system develops, accompanied by stasis and thrombosis of the venous system with overloading of the lymphatic drainage from the part. As the part is superficially warmed, the surface cells warm first, even while vascular impairment exists. Because the surface tissue is inadequately nourished and because its cellular metabolites build up, tissue death ensues. The variables affecting this chain of events then are duration and severity of the cold stimulus, and the individual's reaction to injury.

Several clinical syndromes may result from cold injury. *Chilblains* are the result of severe peripheral vasospasm with warming of the part before the circulation has recovered, with subsequent minimum cell death. The later inflammatory reaction may be prolonged by a repetition of the initiating trauma. *Immersion foot* is the result of prolonged vasospasm from a relatively mild but prolonged

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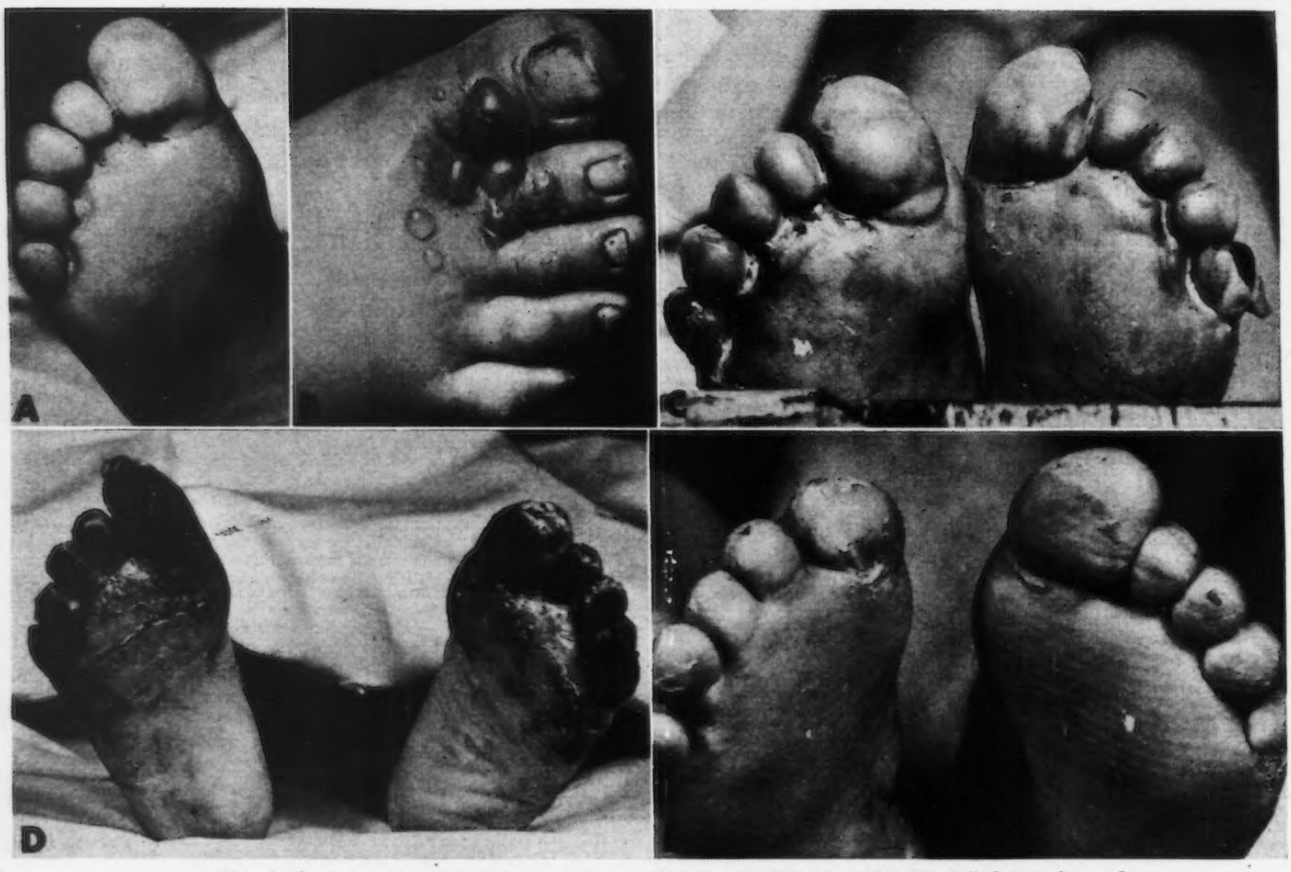

Fig. 1: Case 1.—(A) and (B) Appearance of feet on admission. (C) Feet 5 days after admission. (D) 10 days after admission. (E) Final result 12 weeks after injury.

cold stimulus with moderate to severe tissue necrosis depending upon the degree of retrograde arterial and/or venous thrombosis supervening. *Frank necrosis* of the distal portion of an extremity is the result of severe cold injury together with profound vasoconstriction and thrombosis. The portion will never recover spontaneously, but if therapy is directed initially towards prevention or reduction of vasospasm and thrombosis with thawing of the frozen part from within outward, much damaged tissue may be saved.

Lumbar sympathectomy effectively interrupts sympathetic stimuli to the lower extremities, but carries with it certain operative risks, including orthostatic hypotension, back pain, and loss of ejaculation in the male.[1]

Paravertebral lumbar sympathetic block is also effective and carries less risk. A single injection of a local anesthetic agent lasts only one to three hours;[2] the effect required for our purpose must be more prolonged, however. Continuous epidural analgesia combines the advantages of both methods: it is simple, reversible and carries little risk.

The concept of epidural analgesia was first introduced in 1901, and sporadic reports of the use of this method appeared in the literature thereafter. It was not until the early 1950's that it came into wide use for surgical analgesia. Epidural anesthesia makes use of the fact that nerve fibres differ in size, function and anesthetic susceptibilities. Fibres of small diameter have a relatively large absorptive area in relation to their volume, and little or no myelin sheath. They are, therefore, more susceptible to the effects of local anesthetic agents than are the larger fibres. Because of this, differential blocks are possible by using varying concentrations of local anesthetic agents. One may selectively block autonomic pathways alone, or also block sensory fibres but spare motor fibres.[3]

Three cases of frostbite of the lower extremities were recently treated by the authors.

CASE 1.—A man, aged 47, was admitted to St. Michael's Hospital, Toronto, six hours after leaving a box car in which he had travelled, over a period of three days, from Winnipeg to Toronto. He had previously been well. On admission, both lower extremities to the knees were swollen and puffy with a grey cyanotic skin colour; early blistering was present (Fig. 1a and b).

A continuous epidural block was started on admission, using Carbocaine 2%, 15 c.c. every 6 hours. The catheter was placed in the L2-L3 interspace; the block was continued for four days. In addition he was given a high protein, high caloric diet, spiritus frumenti 2 oz. every 4 hours, and erythromycin, orally, 250 mg. every 6 hours. Heparin was given intravenously at a rate which tripled the clotting time, and phenindione (Danilone) was given orally in quantities which tripled the prothrombin time. Heparin was discontinued when the phenindione had taken effect. Local treatment consisted of a cool atmosphere about the

lower limbs, hot water bottles to the abdomen and complete bed rest. There was an immediate increase in skin temperature in the limbs and the grey-blue colour was replaced by pinkish red.

By five days the edema was subsiding. There was marked blistering and superficial skin gangrene of both forefeet (Fig. 1c). Twenty-four hours after discontinuing the block it was noticed that the skin temperature dropped. Venous dilatation, which had been marked while the continuous epidural analgesic was being used, was no longer present, and the cyanosis of the leg below the knee returned. Because of this, a second epidural block was started at the L2-L3 interspace on the sixth day after injury and continued to the tenth day. Again Carbocaine 2%, 15 c.c. every 6 hours, was used, with an immediate improvement in the peripheral skin temperature and colour and a decrease in peripheral pain.

By ten days there was no edema, but the superficial skin gangrene had progressed (Fig. 1d). At this time, he was taken to the operating room and a cross-foot flap from the left instep to the right great toe was carried out. This enabled us to save all possible length in this digit. In addition, the second and third toes on the right foot were amputated through the proximal interphalangeal joints. Ten days later, the flap was divided and the flexor surface of the left great toe was resurfaced with a cross-foot flap. This too was divided at ten days.

The patient was sent home five weeks after injury. His feet 12 weeks after injury are shown in Fig. 1e.

CASE 2.—A man, aged 47, was admitted to St. Michael's Hospital, Toronto, five days after freezing his feet by overnight exposure in a snowbound car. He had previously been well. He stated that initially, on warming, his feet appeared normal. Over the next 48 hours they gradually became cyanosed and swollen. He was treated in a local hospital for three days with bed rest, during which time the condition of the feet became worse. He was referred for definitive therapy.

On admission there was superficial gangrene of the skin of the toes accompanied by edema of the feet to the ankles (Fig. 2a). The skin was grey and cold. Again on admission a continuous epidural block using Carbocaine 2%, 15 c.c. every 6 hours, was started. The catheter was placed in the L2-L3 interspace. This block was continued for four days.

Supportive therapy similar to that in Case 1 was used.

Ten days after injury—that is, five days after admission to St. Michael's Hospital—the edema had subsided. There was well-demarcated gangrene of the toes (Fig. 2b).

Twenty-four hours after cessation of the continuous epidural analgesic, the extremities below the knee again became cold and cyanosed. A second epidural block at the L2-L3 interspace was started on the sixth day after admission, and continued for four days. Carbocaine 2% in similar dosage was used.

At this time operation was carried out. On the right foot, the great toe was amputated through the metatarsal-phalangeal joint and the second and third toes were amputated through the distal interphalangeal joints. On the left foot, the great toe was amputated through the interphalangeal joint, and, to conserve length, a cross-foot flap was used to resurface the end of the stump. The second and third toes were amputated through the distal interphalangeal joints.

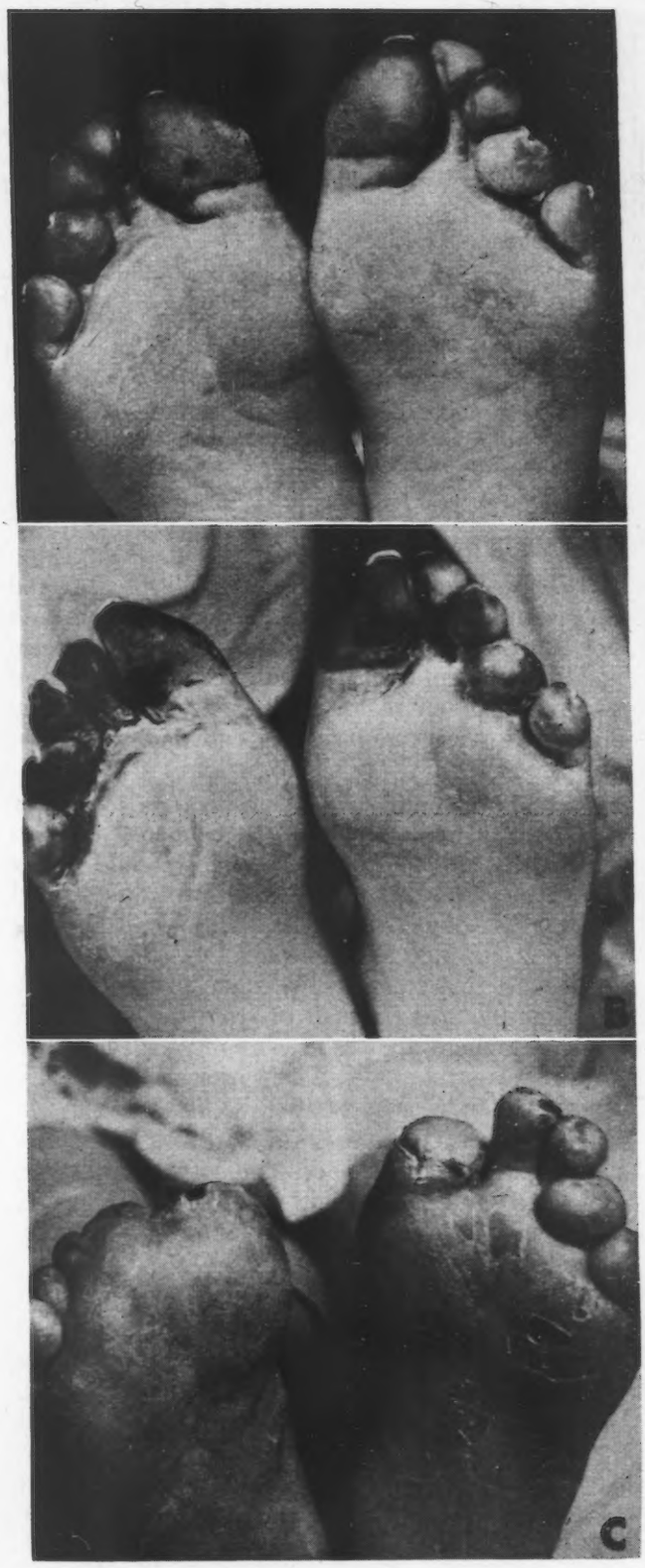

Fig. 2: Case 2.—(A) Appearance of feet on admission (5 days after injury). (B) Feet 5 days after admission. (C) Feet at time of discharge, 6 weeks after injury.

The cross-foot flap was divided after 18 days.

The appearance of the feet on discharge six weeks after injury is shown in Fig. 2c.

CASE 3.—A man, aged 66, was admitted to St. Michael's Hospital, Toronto, approximately four weeks after injury. He had been an alcoholic for 18 years. His left foot had been frozen; the right was normal. The left great toe was gangrenous to the metatarsal-phalangeal joint, as were the second and third toes. Immediately proximal to the gangrene was a rim of inflammation, but there was no edema of the foot. Skin temperature was normal.

Treatment consisted of a continuous epidural block at the L2-L3 interspace using Carbocaine 2%. General supportive therapy was similar to that given the first two patients. Treatment had no effect on the toes, and amputation of the great, second, and third toes of the left foot through the metatarsal-phalangeal joints was carried out four days after admission. Six days later the patient discharged himself from hospital.

DISCUSSION

The treatment of frostbite should be directed towards thawing the frozen part from within and not by external warming. The relief of vasospasm and the prevention of thrombosis with maximum restoration of circulatory efficiency should be the initial aim to accomplish this end and should be instituted early.

Continuous epidural analgesia plus whatever effect is obtained from spiritus frumenti and, reflexly, from heating the abdomen, should effectively alleviate the vasospastic element to cold injury in the lower limbs. In addition, all possible collateral vascular channels to the area will be opened up, and warming will take place from the inside of the part, instead of from the surface. A cool atmosphere about the extremity will aid this. Anticoagulant therapy will help prevent thrombosis. Thus frank tissue necrosis will be limited.

The first case illustrates dramatically the effects of vasospasm in cold injury. The cold stimulus was prolonged (three days) and vasospasm was severe. Treatment was instituted early and was effective; tissue loss was minimal.

The second case illustrates the effect of vasospasm developing from relatively short but severe cold injury (eight hours). Initial tissue damage was slight, but the resulting vasospasm was severe. This plus retrograde thrombosis in the arterial system and venous and lymphatic stasis contributed to considerable tissue loss. Early vigorous spasmolytic and anticoagulant therapy might have improved the end result.

The third case when seen showed only the end result of the combination of unrelieved vasospasm and thrombosis and, as expected at such a late period, the treatment did not influence the resulting peripheral tissue necrosis.

There is a small but definite risk of epidural bleeding resulting from the catheter being left in place while anticoagulant therapy is being used. This is probably less than the risk from repeated paravertebral lumbar sympathetic blocks or lumbar sympathectomy. No problems from epidural hemorrhage developed in the three cases presented.

Assessment of the effectiveness of treatment in cold injury is extremely difficult but the regimen outlined is rational and appeared to influence markedly the first two patients. We were not surprised at the failure of response in the third case.

SUMMARY

The initial treatment of frostbite should be directed towards warming and thawing the part from within rather than from without. The relief of peripheral vasospasm and the prevention of retrograde arterial and venous thrombosis by use of continuous epidural anesthesia and administration of anticoagulants appears to be an effective method towards accomplishing this end.

Continuous epidural anesthetics were administered by Dr. S. O'Rourke and the resident anesthetic staff of St. Michael's Hospital.

REFERENCES

1. BLAKEMORE, W. S. AND COOPER, D. Y.: *S. Clin. North America*, **37**: 1575, 1957.
2. MOORE, D. C.: Regional block, 2nd ed., Charles C Thomas, Springfield, Ill., 1957.
3. BROMAGE, P. R.: Spinal epidural analgesia, E. & S. Livingstone Ltd., Edinburgh, 1954.

TELEPHONE TIPS FOR RECEPTIONISTS

Telephone courtesy, important anywhere, is a definite "must" in a doctor's office where slipshod telephone manners on the part of a nurse or receptionist can reflect unfavourably on the practitioner.

An impolite or indifferent receptionist will give a prospective patient the impression that he is "just another case", hardly inspiring any confidence in him. He may not want to see the doctor if his first contact is through a careless staff. He may revise a previous good opinion if he thinks that the doctor permits careless or impolite personnel to work for him.

This, of course, applies not only to prospective patients, but to the regular practice also. A slow resentment builds up in a person if he is not given the consideration he has a right to expect, and whether an emergency is on the line or just Mother making an appointment to have little Johnny's tonsils examined, a courteous manner is expected—if not absolutely required—to inspire confidence and reassurance.

While it is assumed that most receptionists are polite on the telephone, it is also true that telephone courtesy requires more than polite language. Here are a few pointers, given by Bell Telephone, that receptionists would do well to remember:

When your telephone rings, answer promptly. This is the first step in showing the caller you are interested in his call.

Identify the person you are answering for—"Dr. McDougall's office". Don't slur the name because *you* are familiar with it; the other party may not be.

Give your own name too, and instructions the doctor has given you, if he is out.

Do not try to alter your voice, but talk clearly in a conversational manner *directly into* the mouthpiece. The telephone company points out that the instrument is *designed* to be used this way.

Do not talk too fast, and never talk with anything in your mouth; it clutters up your speech and makes it hard for the person to understand you.

Remember, if you are a receptionist, you can't afford to be indifferent—nor can the doctor you work for afford to let you be.—*The Canadian Doctor.*

THERAPEUTIC TRIAL OF A NEW ORAL DIURETIC*

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S. J. SHANE, M.D., F.R.C.P.[C], *Halifax, N.S.*

UNTIL 10 YEARS AGO, the only effective diuretics available for clinical use were the mercurial and the theophylline derivatives. The former were effective, but had the disadvantage that parenteral administration was required; the latter were only mildly effective. In 1949, Schwartz[1] described the diuretic effect of the sulfonamides, which led to the development of acetazolamide, the first of the carbonic anhydrase inhibitors to be used in this connection.

Further progress was made in 1957, the aromatic sulfonamide chlorothiazide being synthesized at that time. Since then a host of similar drugs with comparable actions has been developed.

Recently the Geigy Laboratories reported effective diuretic action from sulfonamylated bezophenone derivatives, G33182 (1-oxo-3-(3'-sulfamyl-4-chlorphenyl)-3-hydroxyisoindoline) being one of these (see Fig. 1). The mode of action of this

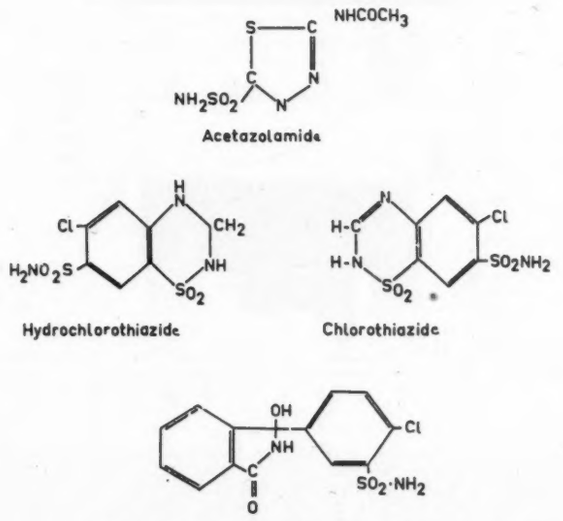

Fig. 1.—Chemical formula of G33182 (Hygroton) compared with formulae of hydrochlorothiazide, chlorothiazide and acetazolamide.

preparation is thought to be similar to that of chlorothiazide, i.e. a minor carbonic-anhydrase-inhibiting effect, together with major inhibition of Na^+ and Cl^- reabsorption in the proximal convoluted tubules.[2]

The purpose of this study was to determine the effectiveness of G33182 in patients with refractory edema. In all, five patients were studied. Two had atherosclerotic heart disease with congestive heart failure, one had constrictive pericarditis, one suffered from chronic rheumatic heart disease with mitral insufficiency and congestive heart failure, and one patient had congestive heart failure of as yet undetermined origin.*

The patients were chosen from patients routinely admitted to the Victoria General Hospital, Halifax, Nova Scotia, because of congestive heart failure with edema. When it was apparent that a patient was not responding to treatment, he was transferred to the metabolism service. Serum sodium, potassium and chloride determinations were performed three times weekly, accurate fluid balance records kept and 24-hour urine specimens collected for sodium, potassium and chloride determinations. The state of water balance was calculated by subtracting the sum of the urinary output, plus 300 ml. for insensible loss, plus other determined losses, from the total fluid intake. After a control period of two days, other diuretics were discontinued and G33182 was started. Weekly hemograms were made to discover hemopoietic disturbances.

CASE REPORTS

CASE 1.—J.M., a 76-year-old white male with constrictive pericarditis, had been on a low salt diet and chlorothiazide, 500 mg. twice daily, at home. He was admitted to hospital because of increasing edema. On admission on February 15, 1960, he had gross pitting edema up to the umbilicus. He was given a low salt diet (less than 0.5 g.) (see Fig. 2a). On February 20, investigation was begun and, after two control days, he was given G33182, 100 mg. daily, which was continued to February 29, when it was increased to 100 mg. twice daily. On March 7, the patient developed a severe cellulitis of the legs with fever, confusion and urinary and fecal incontinence. The diuretic was continued, although detailed biochemical study could not be carried out after this date. However, the patient lost 25 lb. over a period of 22 days (more than 1 lb. per day). It will be noted that there was marked sodium and chloride diuresis, which reached its peak 48 hours after administration of the first dose. The serum chloride and sodium levels remained relatively constant and within normal limits. There was an actual decrease in the urinary potassium from the control values (from 100 mEq./day to 50 mEq./day), suggesting that G33182 had less kaliuretic effect than chlorothiazide in this patient. A fall in serum potassium was also noted, and for this we have no explanation. At no time did the patient develop signs of hypokalemia. He recovered from the cellulitis and was sent home edema-free 43 days after admission.

CASE 2.—H.G., a 41-year-old male suffering from chronic rheumatic heart disease with mitral insufficiency and congestive heart failure, was admitted on September 25, 1959, with gross dependent edema and pulmonary congestion. He had been treated by digitalis and chlorothiazide on an outpatient basis, but had failed to respond. On admission he was treated by 0.5 mg. digoxin, 2 c.c. Neptal daily, a 0.5-g. salt

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This study was supported, in part, by a grant from the J. R. Geigy Company of Canada.
†Research Fellow in Cardiology, Victoria General Hospital, Halifax, N.S. Dr. Beanlands is supported, in part, by a grant from the National Heart Foundation of Canada.

*Patient A.L.R. was originally thought to have mitral insufficiency due to rupture of a chorda tendinea. More recent evidence suggests the possibility of a cardiomyopathy.

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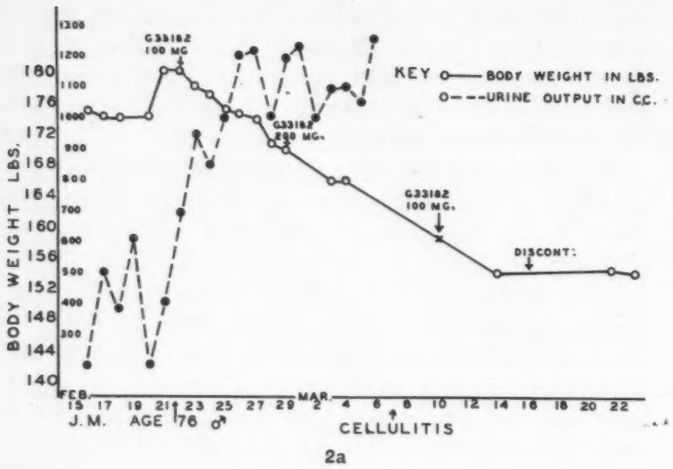

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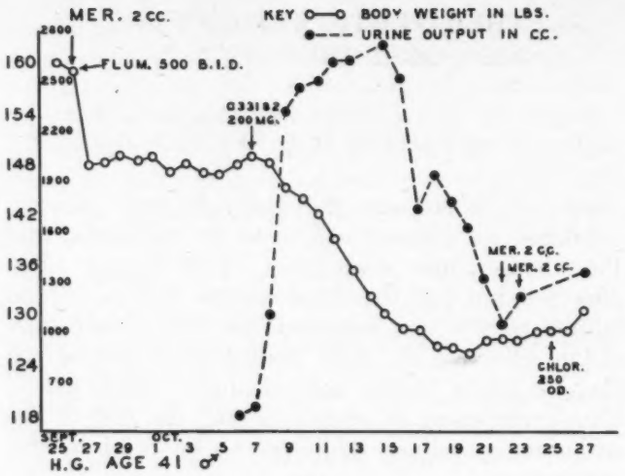

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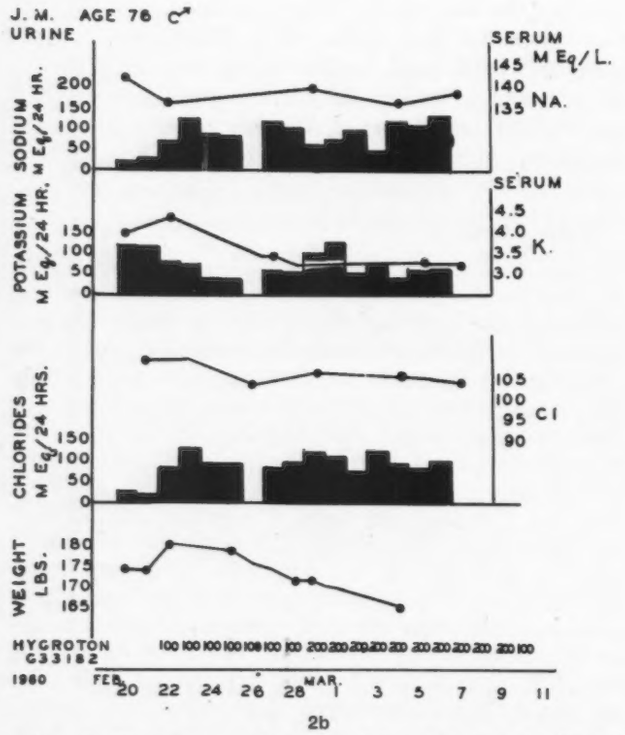

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Fig. 2—Electrolyte and water balance values in Case 1 (J.M.); (a) shows the body weight and urine volume during the patient's hospital stay, (b) shows the water and electrolyte balance during the period of detailed study. G33182 was started on February 22 and continued to March 16. The varying dosages are as indicated on the graphs. Note the increased urine volume, sodium and chloride excretion, and the rapid fall in weight after initiating therapy with G33182.

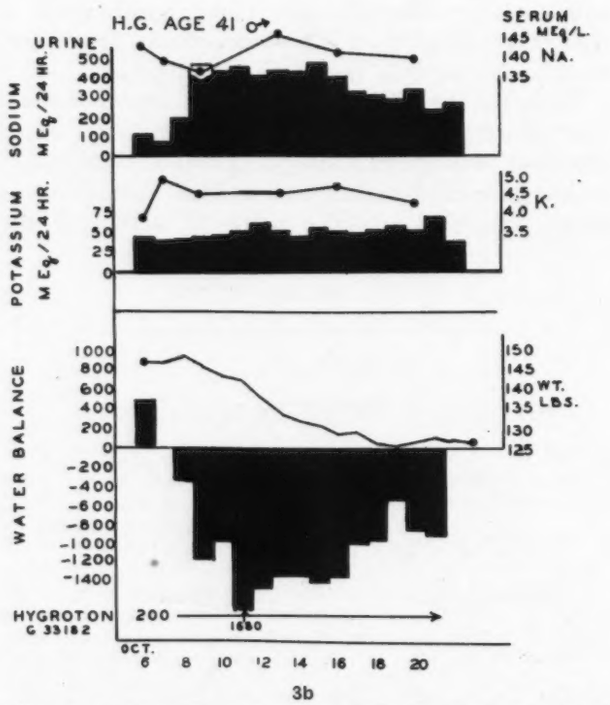

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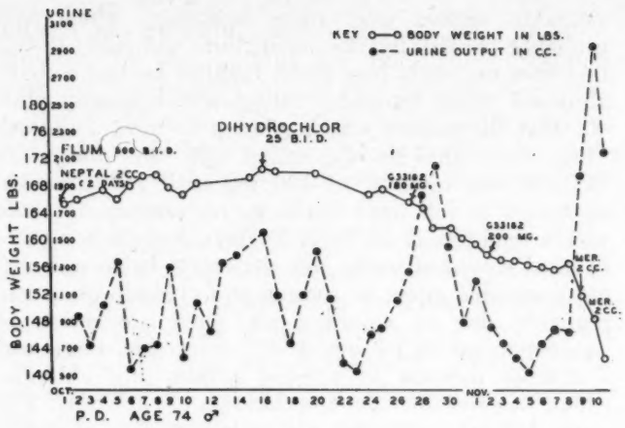
Fig. 3.—Electrolyte and water balance values in Case 2 (H.G.); (a) shows the body weight and urine volume during the patient's hospital stay; (b) shows the water and electrolyte balance during the period of detailed study. G33182 was started on October 7 and continued to October 21. Note the marked increase in urine volume, and sodium and chloride excretion, the rapid fall in weight and the negative water balance after therapy with G33182 was initiated.

diet, and 500 mg. flumethiazide twice daily. On this regimen he lost 12 lb. in three days. His weight became stable at 148-149 lb., but gross edema persisted. On October 5, he was transferred to the metabolic ward. All previous diuretics were discontinued on October 7, and he was started on G33182 on that date. Fig. 3a shows that he had an immediate striking increase in urine volume and a loss in weight of 22 lb. in 11 days. When it was considered that "dry" weight had been achieved, he was given 2 c.c. Thiomerin on two successive days without further diuresis. Fig. 3b gives a detailed account of the patient's water and electrolyte balance. The marked sodium diuresis, reaching a peak 48 hours after the initial dose, should be noted. Chloride values are not available for this patient, owing to a laboratory error. The serum sodium and potassium values remained relatively constant, and there was only a slight increase in potassium excretion. It will also be noted that the patient was in negative water balance throughout treatment to a maximum of 1680 ml. on October 11, 1960. It can be seen that the urinary sodium excretion is obviously too high for the amount of sodium the patient was receiving. The reason for this is uncertain, although the authors feel that it is probably due to a laboratory error. At any rate, if there *is* an error, it is mirrored in all sodium determinations on this patient.

CASE 3.—P.D., a 74-year-old white male, was admitted to the Victoria General Hospital on October 1, 1959, with a diagnosis of atherosclerotic heart disease with congestive failure and moderate dependent edema. He was given digoxin 0.25 mg. daily, a 0.5-g. salt diet, Neptal 2 c.c. daily for 2 days and



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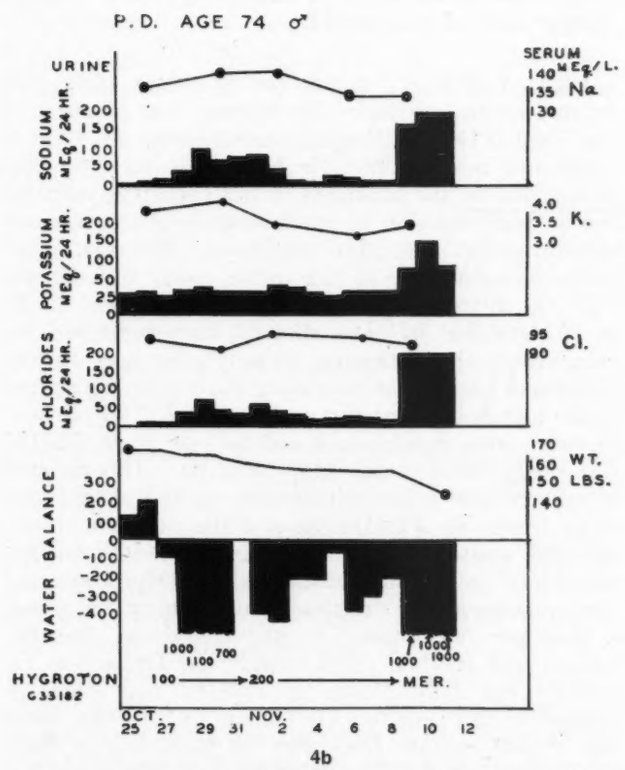

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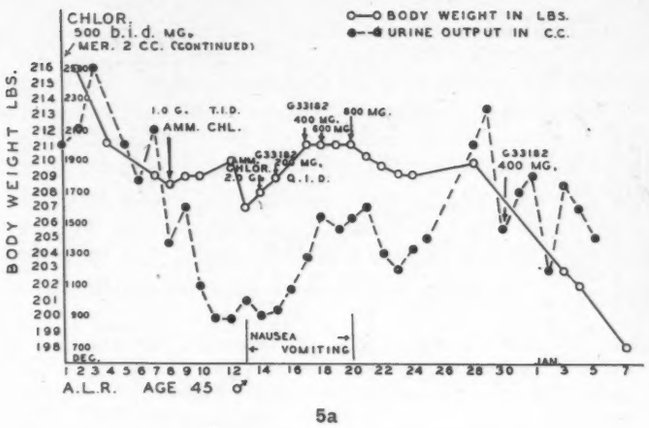
Fig. 4.—Electrolyte and water balance values in Case 3 (P.D.); (a) shows the body weight and urine volume during the patient's hospital stay and (b) shows the water and electrolyte balance during the period of detailed study. G33182, 100 mg. daily, was started on October 27, increased to 200 mg. daily on November 1 and discontinued November 8. Note the decrease in weight, increase in urine volume, and sodium and chloride excretion, and the negative water balance after initiating therapy with G33182. Note also the marked effect of the mercurial given on November 8 and November 9.



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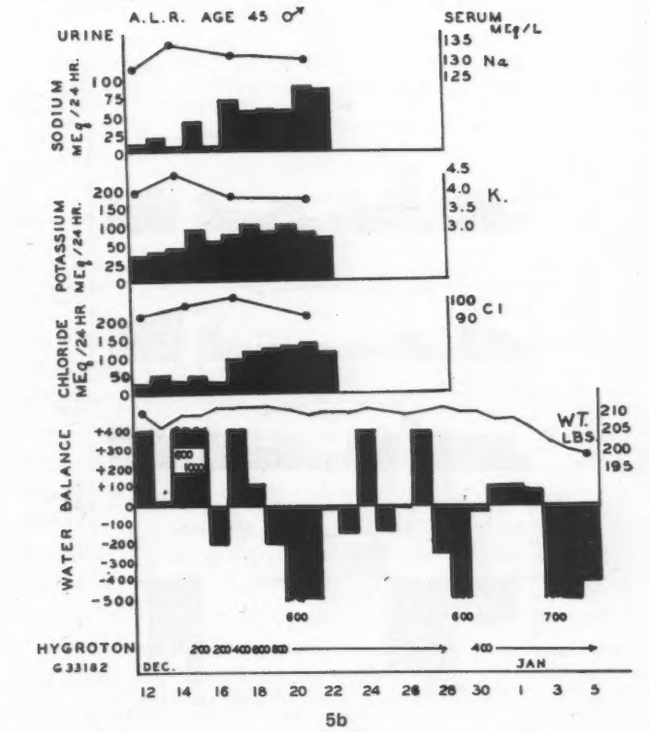

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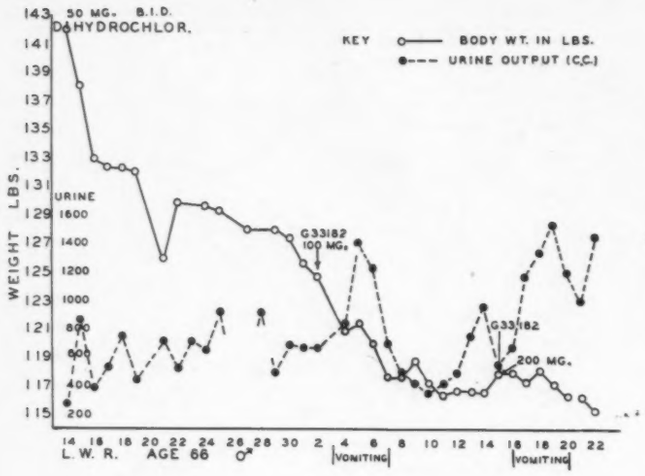
Fig. 5.—Electrolyte and water balance values in Case 4 (A.L.R.); (a) shows the body weight and urine volume and electrolyte balance during the period of detailed study. during the patient's hospital stay and (b) shows the water G33182, 200 mg. daily, was started on December 15, increased to a maximum of 800 mg. on December 19 and reduced to 400 mg. on December 30. The absence of diuresis between December 13 and December 20 was probably due to the vomiting and subsequent loss of medication. It should be noted that there was a marked saluresis starting on December 17 and subsequently a gradual loss of weight.

flumethiazide 500 mg. twice daily, with no appreciable change in body weight. On October 16, flumethiazide was discontinued and hydrochlorothiazide 25 mg. b.i.d. was given, with no diuresis. On October 25 he was transferred to the metabolism ward, and on October 27 all diuretics were discontinued, and he was treated by G33182, 100 mg. daily, increased to 200 mg. daily on November 1 (Fig. 4a). There was an immediate increase in urine volume and a weight loss of 10 lb. over a 10-day period. By November 8, the patient was considered "dry", but the administration of Thiomerin (2 c.c.) resulted in further considerable diuresis. The details of the water and electrolyte balance can be seen in Fig. 4b. The sodium and chloride diuresis reached its peak 72 hours after the initial dose, and there was a slight increase in potassium excretion. The serum sodium and chloride remained relatively constant, but there was a slight decrease in potassium. The patient was in negative water balance to the extent of 1100 c.c. by the 4th day of treatment. The striking effect of the mercurial diuretic can also be noted. This patient expired suddenly on November 11, with no apparent cause. Postmortem examination revealed atherosclerotic cardiovascular disease, bronchopneumonia, and old cerebral softening, but no explanation for the sudden demise was found.

CASE 4.—A.L.R., a 45-year-old male with mitral insufficiency, was admitted to the Victoria General Hospital on December 1, 1959, in moderate congestive heart failure. He had been treated by digitalis and chlorothiazide as an outpatient, but these had failed to control his edema. On admission, chlorothiazide



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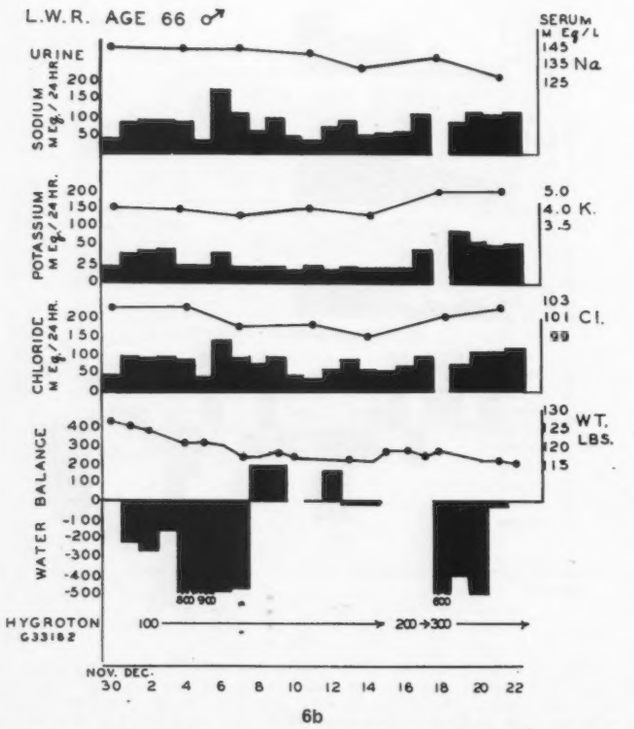

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Fig. 6.—Electrolyte and water balance values in Case 5 (L.W.R.); (a) shows the body weight and urine volume during the patient's hospital stay, (b) shows the water and electrolyte balance during the period of detailed study. G33182, 100 mg. daily, was started on December 2 and continued to December 15, when it was increased to 200 mg. and subsequently increased to 300 mg. on December 18. Note the slight increase in sodium and chloride excretion and the negative water balance after initiation of therapy.

500 mg. twice daily and digoxin 0.25 mg. daily were continued, and a 0.5-g. salt diet and Thiomerin 2 c.c. daily were started. Fig. 5a shows that this regimen resulted in a 7-lb. weight loss over an eight-day period. On December 8, ammonium chloride 1.0 g. thrice daily was started because of a low serum chloride value and the absence of diuresis. The dosage was increased on December 14 to 2.0 g. four times a day, with no effective diuresis.

The patient was then transferred to the metabolic ward, and on December 15, all previous diuretics including ammonium chloride were discontinued, and G33182 in a dosage of 200 mg. b.i.d. was given. This was increased gradually, so that by December 19 the dose was 800 mg. daily. It should be noted, however, that from December 13 to 20, the patient had considerable nausea and some vomiting, which was probably caused by the ammonium chloride. It was therefore uncertain how much G33182 he had actually absorbed. From December 20 onward, it became obvious that the patient was beginning to have a diuresis (Fig. 5a), and on December 30, the dosage of G33182 was reduced to 400 mg. daily. The weight continued to fall until discharge on January 7, 1960, with a total loss of 12 lb. in 17 days. Fig. 5b is a more detailed record of water and electrolyte balance, showing a variable effect on sodium and chloride excretion, probably due to vomiting and poor absorption of medication up to December 17. After this, there was a definite increase in urinary sodium and chloride, which was sustained for the duration of the study. The water balance, although not as consistently negative as in some of the other patients, was clearly negative during most of this period.

CASE 5.—L.W.R., a 66-year-old white male with atherosclerotic cardiovascular disease, was admitted to the Victoria General Hospital on November 14, 1959, in congestive heart failure. He had had several previous admissions for the treatment of this condition, responding on each occasion to administration of digitalis and chlorothiazide. On this admission, he was given hydrochlorothiazide, 25 mg. twice daily, and digoxin, 0.25 mg. twice daily. On this regimen, he lost 13 lb. in 12 days, but by November 26 his weight had become relatively stationary, although he had obvious dependent edema. On November 30, he was transferred to the metabolic ward and on December 2, all previous diuretics were discontinued and he was given G33182 in a dosage of 100 mg. daily (Fig. 6a). This resulted in an increased urine volume and marked weight loss. From December 3 to December 7 the patient had considerable nausea and vomiting, considered to be due to G33182, but readily controlled by chlorpromazine. The exact amount of drug assimilated during this period is therefore not known. It was considered that the patient had reached "dry" weight on December 11, because the daily dosage of G33182 had been increased to 200 mg. on December 15 with no effect and to 300 mg. on December 18 with only a slight decrease in weight. This increase in dosage caused a recurrence of the nausea and vomiting, thus supporting the previous impression. The patient left hospital against advice, before further studies could be carried out.

DISCUSSION

There is no doubt that G33182 is a potent diuretic. In all five patients, who had not responded to the administration of chlorothiazide, hydrochlorothiazide, flumethiazide and mercurials, G33182 produced a diuresis. This effect was marked in two patients and moderate in three. No patient lost less than 12 lb. during the period of observation, despite the fact that all patients had previously received adequate doses of well-known diuretics.

The drug had a selective effect on sodium and chloride excretion, causing as much as 400 mEq. of sodium to be excreted in 24 hours. The effect on potassium excretion was variable. Two patients had a diminution in potassium excretion by comparison

with that resulting from use of the previous diuretic. In one patient the potassium excretion remained unchanged, and in two patients there was a slight increase. The peak effect appeared to occur 48 to 72 hours after administration, suggesting that the drug need be administered only on alternate days.

The dosage varied from 100 mg. to 800 mg. daily. Two patients had nausea and vomiting, which in one patient was considered to be from other causes, while in the other it appeared to be due to the diuretic. This was, however, easily controlled by chlorpromazine. No evidence of bone marrow depression was noted.

SUMMARY

Five patients with congestive heart failure and edema, shown to be "refractory", were subsequently treated by G33182. Detailed fluid and electrolyte balance studies were carried out. All subjects had a significant diuresis, although their condition had been stationary on their previous regimen. There was a selective excretion of sodium and chloride with little or no effect on potassium. One patient had nausea and vomiting which was readily controlled by administration of chlorpromazine. There were no other undesirable side effects. It would appear that G33182 is a potent diuretic with minimal side effects.

The authors express their appreciation to Dr. R. M. MacDonald for permission to carry out balance studies on patient J.M.; and to Dr. W. I. Morse for his invaluable advice and encouragement.

REFERENCES

1. SCHWARTZ, W. B.: *New England J. Med.*, **240**: 173, 1949.
2. STENGER, E. G., WIRZ, H. AND PULVER, R.: *Schweiz. med. Wchnschr.*, **89**: 1126, 1959.

EXPERIMENTAL STUDIES ON VAGINAL BLEEDING AT OVULATION TIME*

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RECENT OBSERVATIONS on ovulation bleeding in humans suggest that the actual day of ovulation can be determined by simple, inexpensive methods.[1] Some authors suggest, however, that the typical intermenstrual spotting which comes at mid-cycle may not be blood at all but may actually be follicular fluid.[2] In order to study this problem further, it seemed desirable to conduct experiments in animals, since, in humans, suitable vaginal samples are not readily obtained and the necessary surgical procedures are not permissible. Although it is recognized that findings in animals do not necessarily apply to humans, the albino rat seemed an ideal test animal. It has a short estrous cycle, the stages of which can be accurately determined by examination of vaginal smears.

The estrous cycle in the albino rat as described by Long and Evans[3] extends over four to five days, and is divided into five stages. Proestrous, or Stage I, is approximately 12 hours in duration and is the phase during which the graafian follicle enlarges. Estrus, the time when the female is receptive to the male, is a period averaging 10 hours, beginning in the last part of Stage I and occupying most of Stage II. Stages III and IV correspond to metestrus and together extend for approximately 24 hours. Ovulation occurs in Stage III and the uterine epithelium undergoes vacuolar degeneration. In Stage IV the ova are in the oviduct and vacuolar degeneration of the epithelium is continued. There is an accompanying epithelial regeneration and replacement. Uterine hemorrhage or menstrual bleeding is not observed in the rat. Stage V (diestrous) is approximately 57 hours in duration, during which time the ova traverse the oviduct.

Ovulation occurs in Wistar albino rats approximately eight hours after the beginning of heat in mated females and slightly later in non-mated animals.[4] The segmenting ova enter the uterus between 95 and 100 hours after ovulation.[5] Unfertilized ova usually degenerate in the proximal loops of the oviduct.[3] Since ovulation occurs during Stage III of the cycle and the ova do not reach the uterus for 95 to 100 hours, it would seem probable that blood in the vagina from one ovulation period would be observed in Stage IV or V of the next cycle. The studies reported herein were conducted to ascertain whether blood cells are present in samples of vaginal washings collected from rats during various stages of the estrous cycle, and to determine if blood cells accompany or precede the ova in their passage through the genital tract.

MATERIALS AND METHODS

Sexually mature, virgin female, albino rats of the Food and Drug strain were used.

Vaginal washings were taken by gently injecting 0.2 ml. warm physiological saline into the vagina, using a 1-ml. serological pipette, and allowing the saline to flow back into the pipette.

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Hematest* and Occultest* tablets were used to detect occult blood in vaginal samples.

Unstained slides of vaginal smears and washings were examined by phase contrast microscopy. Smears were stained with Giemsa, Wright's, hematoxylin-eosin, and Papanicolaou stains.[6] The peroxidase reaction of Lepehne for erythrocytes,[7] Dunn-Thompson hemoglobin stain[8] and Turnbull's blue method for hemosiderin[9] were used to detect red blood cell fragments and red blood cell breakdown products.

Vaginal washings were taken from 10 rats on 10 consecutive days. In addition single vaginal washings were taken from 100 rats. The stage of the cycle was determined in each instance and the samples were examined as described above.

Oophorectomies were performed on 10 animals. Vaginal washings were taken for five consecutive days on these animals one month and two months postoperatively. Hysterectomies were performed on 10 animals and vaginal washings were tested as for the ovariectomized animals. In further studies, fallopian tube ligations were performed on 10 animals. Two animals were examined each week on consecutive weeks after the operation. After four weeks, the ovaries and fallopian tubes were taken for microscopic and macroscopic examination.

The ovaries and fallopian tubes were taken from five animals in late Stage II or Stage III of the cycle, that is, at ovulation time. With the aid of a stereoscopic microscope, a drawn glass pipette was inserted in the periovarial opening and the fluid in the periovarial space was removed and examined for the presence of red blood cells. In other animals in late Stage II or Stage III of the cycle, the ovary on one side was exposed and the fluid from the periovarial space was removed and mixed with 10 λ of fresh autologous blood from the caudal vein. The mixture was then injected into the periovarial space, distending the periovarial sac. Vaginal washings were taken every eight hours for the next 144 hours and examined for the presence of erythrocytes. The animals were then sacrificed.

The uterus was exposed in five animals and 20 λ of autologous blood was injected into the uterus at the uterotubal junction. Vaginal washings were taken at hourly intervals for 36 hours and examined for the presence of red blood cells.

The oviducts were taken from 10 animals, 5 of which were in late Stage III or Stage IV of the cycle. In these animals the ova would be in the first loops of the oviduct. The oviducts from the remaining 5 animals were taken 70 to 85 hours after ovulation had occurred. Serial sections were prepared from the oviducts of the 10 animals and were examined for the presence of red blood cells around the ova and their corona cells.

*Hematest and Occultest tablets were supplied by Ames Company of Canada Limited.

RESULTS

Vaginal Washings

A positive reaction with the test tablets depends on the presence of peroxidase in the material under test. Red cells do not contain peroxidase but possess peroxidase activity.[10]

Table I shows the number of animals in each stage of the cycle, the number of positive reactions to test tablets in each group, and the percentage of the total number of positive reactions found in each stage of the cycle.

The results show that the great majority of positive reactions were obtained with animals in Stages IV or V of the cycle, although animals in these stages did not invariably show positive reactions. In animals in Stage IV or V of the cycle which did not give a positive reaction the vaginal washings were clear, with few cells present. If the sample was cloudy or contained stringy mucus, a positive reaction was invariably observed. The small number of positive reactions observed in animals in Stage III were from animals which exhibited gross hematuria. It is probable that the positive reaction in these animals resulted from contamination of the sample from blood in the urine.

In the samples showing positive reactions, no red blood cells were observed either in wet or stained smears; the predominant cell was the polymorphonuclear neutrophil. When the vaginal washings were mucous in nature and leukocytes were numerous, a strong positive reaction to the test tablets was usually observed within 15 seconds. Since most of the washings giving positive reactions apparently contained no whole red blood cells, the washings were examined for red blood cell fragments, hemoglobin and hemosiderin. Smears made from vaginal washings which were strongly positive to test tablets in 15 seconds were negative to the peroxidase reaction of Lepehne for erythrocytes, Dunn-Thompson hemoglobin stain and Turnbull's blue method for hemosiderin.

These findings did not rule out the possibility that lysed red blood cells were present in a concentration low enough to give negative reactions to the stains but high enough to give positive Occultest reactions. To rule out the possibility of significant differences in sensitivity, rats' blood was hemolyzed with distilled water and parallel determinations were made employing both test tablets and the peroxidase reaction of Lepehne. It was found that dilutions which took as long as 60 seconds to show a positive test stained positive for hemoglobin. These results indicate that the positive reaction obtained with the vaginal washings was not due to the products of lysed erythrocytes. It is probable that positive reactions were due to the presence of leukocytes, which contain a peroxidase.[11] A positive reaction to leukocytes was observed microscopically in samples of vaginal washings containing large numbers of white blood cells.

TABLE I.—REACTIONS OF VAGINAL WASHINGS TO TEST TABLETS

	Number of animals in each stage of cycle				*Number of + reactions in each group*				*% + of total + reactions*			
Stage of cycle	*I*	*II*	*III*	*IV and V*	*I*	*II*	*III*	*IV and V*	*I*	*II*	*III*	*IV and V*
10 animals. Washings 10 consecutive days	7	15	22	56	1	0	3	32	2.8	0	8.3	88.9
100 animals. Single washing	13	11	15	61	1	0	0	57	1.8	0	0	98.2

Wet smears of such samples were placed on a slide and a test tablet was placed at the periphery of the smear in contact with the fluid. As crystals from the tablet entered the microscopic field there was an instantaneous colour change to dark blue of the leukocytes in the field.

Oophorectomies

The results are given in Table II. Vaginal washings from ovariectomized animals at the one-month and two-month post-operation period consistently revealed leukocytes and epithelial cells upon microscopic examination. Negative reactions to tablets were observed only in those samples which were clear macroscopically and contained very few cells microscopically.

TABLE II.—SAMPLING RESULTS FROM OOPHORECTOMIES AND HYSTERECTOMIES

Postoperative period in days	*Number of samples*	*No. animals in stage IV or V of cycle*	*No. with positive reaction to test tablets*
Oophorectomy			
30 - 35	50	50	41
60 - 65	50	50	46
Hysterectomy			
30 - 35	50	26	23
60 - 65	50	29	27

Hysterectomies

Table II also shows that vaginal smears from animals with hysterectomies revealed normal cycles and the vaginal washings reacted to Occultest in a similar manner to the vaginal smears in the 10 non-operated animals. As was found previously, an average of over 90% of the positive reactions were observed in Stages IV or V of the cycle.

Fallopian Tube Ligations

Postmortem examination showed well-developed cysts on one or both ovaries of all 10 animals. A portion of the fluid content of the cyst was carefully withdrawn under a stereoscope to avoid puncturing the minute blood vessels that covered the cyst. The contents of the cyst were strongly positive with Occultest, and microscopic examination revealed abundant red blood cells in smears of the fluids. In those instances where the sac was distended with fluid, there was an occlusion of the periovarial sac opening by the ligature.

Fluid from the Periovarial Sac at Ovulation Time

At this stage of the cycle the periovarial sac is quite turgid and distended with fluid. The fluid contained numerous red blood cells, indicating that fluid entering the oviduct with the ovum would contain erythrocytes.

Autologous Blood Injected into the Periovarial Sac at Ovulation Time

Vaginal smears taken at eight-hour intervals up to 144 hours postoperatively were consistently negative for red blood cells. At this time, the periovarial sacs were greatly distended with sanguineous-stained fluid. Examination of the opening into the periovarial sac revealed that the edges of the slit-like opening were in apposition. Gentle pressure rendered the opening patent and the fluid in the sac was released. As much as 175 λ of fluid was present in the sac of one animal.

Autologous Blood Injected into the Uterus at the Uterotubal Junction

Whole red blood cells were observed in vaginal washings as early as 2 hours and as late as 27 hours after injection. Since the ova enter the uterus between 95 and 100 hours after ovulation and blood appears as early as two hours after injection at the uterotubal junction, it would be possible that blood from ovulation could appear in the vagina 97 to 102 hours after ovulation.

Oviducts from Animals with Ova in the Ampulla and Isthmus

Serial sections from these animals revealed ova and their corona cells in the first loops of the oviduct. Red blood cells were observed with the corona cells and fluid surrounding the ova, in animals 70 to 85 hours after ovulation (Fig. 1 and 2). The ova showed early signs of fragmentation at this stage. The red cells, however, showed no signs of hemolysis.

DISCUSSION

The results of these experiments indicated that red blood cells apparently accompany the ova through a part of the oviduct and can traverse the genital tract from the uterotubal junction to the vagina.

It has not been established whether red blood cells which are observed accompanying the ova in

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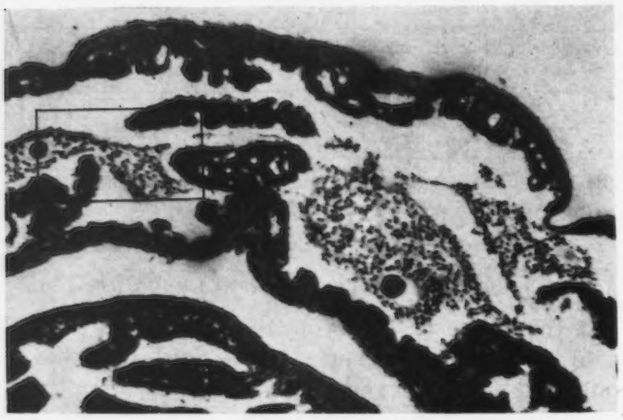

Fig. 1.—Section of oviduct showing three ova with corona cells in the caudal isthmus. Hematoxylin and eosin.

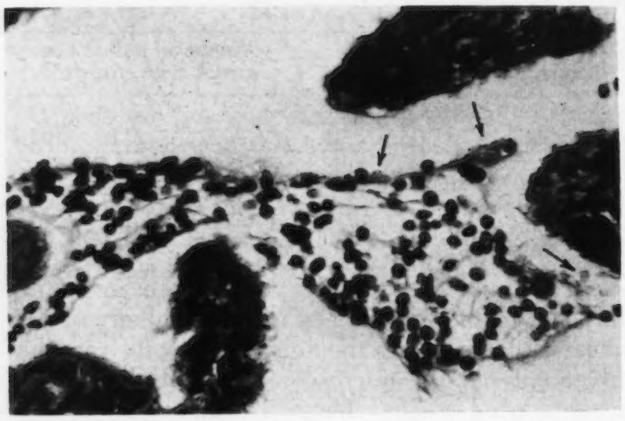

Fig. 2.—Section showing ovum and corona cells (outlined area Fig. 1); arrows point to red blood cells. Hematoxylin and eosin. Yellow filter.

the oviduct pass through the uterus and cervix to reach the vagina.

It is possible that some of these red cells do eventually reach the vagina but are so few in number that they avoid ready detection.

In our rats the positive reaction to test tablets is related to the stage of the estrous cycle rather than blood cells of ovulation or follicular fluid. This is obvious since the reaction was observed in animals with hysterectomies, fallopian tube ligations, ovariectomies and animals experiencing pseudopregnancies. In these animals there was either no follicular fluid or an interrupted passageway. A positive reaction to test tablets in vaginal samples from rats is due to peroxidase-containing white blood cells. It is interesting to note that many of the white blood cells in the washings are viable. The vagina of the rat might serve as a source of white cells for enzyme studies of leukocytes.

SUMMARY

Positive reactions to test tablets for occult blood are observed after ovulation in vaginal washings of rats at the expected time of the estrous cycle. In rats the reaction is due to the presence of leukocytes rather than red blood cells. The white blood cells are present in the animal experiencing a normal cycle as the result of a physiological leukocytosis.

Red blood cells have been found in the corona radiata of the ovum 70 to 85 hours after ovulation.

REFERENCES

1. HURTIG, A.: *Canad. M. A. J.*, **78**: 681, 1958.
2. BIRNBERG, C. H. AND GROSS, M.: *Internat. J. Fertility*, **3**: 374, 1958.
3. LONG, P. A. AND EVANS, H. M.: *Mem. Univ. California*, Vol. 6, 1922.
4. BOLING, J. L. *et al.*: *Anat. Rec.*, **79**: 313, 1941.
5. ALDEN, R. H.: *Ibid.*, **84**: 137, 1942.
6. PAPANICOLAOU, G. N.: *Science*, **95**: 438, 1942.
7. Sandoz atlas of hematology, compiled by E. Undritz, Frobenius Ltd., Basel, Switzerland, English translation, 1952, p. 28.
8. LILLIE, R. D.: Histopathologic technic, The Blakiston Company, Philadelphia, 1948, p. 118.
9. GRIDLEY, M. F.: Manual of histologic and special staining techniques, Armed Forces Institute of Pathology, Washington, D.C., 1957, p. 119.
10. BALDWIN, E.: Dynamic aspects of biochemistry, Cambridge University Press, London, 2nd ed., 1952, p. 167.
11. SUMMER, L. B. AND MYRBACK, K., editors: The enzymes, Academic Press Inc., New York, 1951, Vol. II, Part 1, p. 403.

EXTENDED RESECTION OF BRONCHOGENIC CARCINOMA

Since 1933, surgical resection has provided the most hopeful method of preventing inevitable death from bronchogenic carcinoma. Despite efforts to reduce delay between insidious onset and treatment, the tumour has often advanced beyond the confines of the lung by the time diagnosis has been established. Technical resection of such advanced lesions has become increasingly possible with the use of intrapericardial dissections, bronchoplastic and thoracoplastic reconstruction and new cardiovascular surgical techniques. The reported postoperative mortality, morbidity and length of survival after such extended resection detract from its value. Therefore the differentiation of justified operability from technical resectability remains a problem for critical evaluation. Paralleling the technical improvements in pulmonary resection has been the advance in radiation therapy modalities. The introduction of megavolt generators and more recently cobalt as sources of high energy radiation has enabled the radiation therapist to deliver high tumour doses with reduced morbidity. Though apparent cures are rare and overall survival rates after earlier methods of radiation therapy are discouraging, there is so much room for improvement in management of the patient with advanced lung cancer that the search for better methods of treatment continues.

Based on a study of 200 cases of bronchogenic carcinoma seen and followed up from 1950 to 1959, Lawrence, Walker and Pinker (*New England J. Med.*, 263: 615, 1960) compared their experience with surgical resection and radiation therapy for cure or palliation of bronchogenic carcinoma, with particular reference to the extended lesion. They conclude that surgical resection is the treatment of choice when the carcinoma is grossly confined to the lung. Except in rare circumstances lobectomy is the operation of choice in all lesions not requiring intrapericardial pneumonectomy. Extended pneumonectomy is associated with an increased postoperative mortality and morbidity. Survival rates are not encouraging, and this operation should be reserved for the younger patient who can tolerate it best. Cobalt irradiation therapy administered in selected cases not suited for standard surgical resection provides a hopeful means of palliation and possible cure.

SPECIAL ARTICLE

THE DIAMOND JUBILEE OF THE CANADIAN TUBERCULOSIS ASSOCIATION*

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THIS YEAR the Canadian Tuberculosis Association celebrated the 60th anniversary of its founding. Part of the value of such occasions is that they cause us to look back at the whole road along which a crusade has come, not merely at the section along which each of us individually has travelled. In the case of our Association we see that the advance has been getting better all the time. We are still some distance from the end, and there is a possibility of some dangerous curves ahead, but compared with what the pioneers faced in 1900 our way is well marked and the equipment for keeping it maintained is splendid.

As I studied the records it seemed to me that there were definite stages along the road and that they fell roughly into the pattern of the decades.

I stand in awe of the courage of those who forged ahead in the first years of this century. They started with little to go on but determination. There was no Department of National Health and Welfare to make federal grants for tuberculosis. None of the seven provinces had a health department. There were fewer than 50 tuberculosis treatment beds in the whole Dominion and not one clinic. Ahead lay all the work of organizing local and provincial associations which would rally the public to the need for sanatoria and clinics—and hard work it was, with a public thoroughly convinced that tuberculosis was incurable. The task was to take many years. The success of the undertaking has been demonstrated by the healthy growth of the ten provincial associations and the 183 local associations and committees working from the Yukon to Newfoundland.

Marvellous to relate is that in that first ten years enough public interest was roused and support obtained to get three clinics started which have ministered to tens of thousands, the Royal Edward Institute in Montreal, the Gage Institute in Toronto and the Maycourt in Ottawa. For treatment, patients could go to Muskoka and Hamilton in Ontario, Lake Edward and Grace Dart in Quebec, Brehmer Rest or Tranquille in British Columbia, and Kentville in Nova Scotia.

In 1910, the first year of the second decade, sanatoria were opened in Ottawa, St. Catharines and London, and in Ninette, Manitoba. Most of the patients came with far advanced disease. Despite this, there were enough cures to convince the public that treatment was effective. Slowly but surely the conviction spread that sanatoria should be available as other hospitals were, and that municipalities and provincial governments had responsibility for providing them.

The idea that sanatoria should have government support was given tremendous impetus when thousands of soldiers returning from World War I were known to be suffering from tuberculosis. The Dominion Government built or enlarged sanatoria in every province. It became very plain that with tax support treatment could achieve greater things.

In going over the victories so swiftly I realize that I am not doing justice to the enormous efforts which all this entailed. The efforts to raise funds would make an interesting story by itself. So too would an account of the hundreds of lectures to large crowds and small groups all across Canada. It took eloquence to break down public fatalism.

We would be leaving something out of the picture if we forgot the endless difficulties of operating institutions on insufficient budgets or the always-present problem of patients unable to pay treatment costs.

However, into the twenties they went, having demonstrated that treatment was effective and having obtained tax support for treatment of veterans. This was the first step towards free treatment. Men of vision began to hold it up as the objective, and in 1929 Saskatchewan proclaimed free treatment for tuberculous residents. It was like the first victory in a campaign. It caused rejoicing not only among the victors but among the troops in other sectors. They were convinced that if they kept at it they too would win, and they have. Nowhere in Canada is lack of ability to pay a bar to treatment.

The area in which we could see the most concrete evidence of advance during the twenties was in early diagnosis. Clinics were opened in every province, and not only stationary clinics. It was then that we took to the road. Ontario led with the first travelling clinic in 1923, organized by Dr. G. C. Brink.

In 1927 the Christmas Seal Sale which had been used to finance preventive programs in many cities became nationwide. It did more than provide money. Non-medical people saw how they could help, and they responded with devotion and enthusiasm which have increased with the years. Not only was the Christmas Seal Sale a boon to associations struggling to finance prevention, it also proved to be a wonderful means of getting information to the public on tuberculosis. A good case could be made for the contention that the educational dividends were greater than the financial returns, which is saying a lot.

*From an address to the Executive Council of the Canadian Tuberculosis Association, delivered at Government House, Ottawa, June 26, 1960.

And as to education, this was a period of great expansion. The pamphlets, booklets and posters of the time are in the archives at the present time, but the CTA *Bulletin*, started in 1922, is still going strong.

This was the time too when we drew the Canadian Life Insurance Officers Association into the ranks in a program of tuberculosis control in the Maritime provinces. The stimulus was psychological as well as financial. The result demonstrated that progress could be made even in a high-incidence area. From then on expansion of the work was continuous.

It was at this stage that BCG vaccine was introduced in Canada. It was used first for children of tuberculous patients in Montreal and for nurses in training in Saskatchewan. Indian babies in the Qu'Appelle Valley were also vaccinated. These projects demonstrated that the vaccine had a useful place in preventing the disease in those who would subsequently be exposed to tuberculosis.

And so we came to the thirties, with hopes high even though there were not enough sanatoria, refusing to be discouraged though patients often left before treatment was complete because they could not afford to stay longer, thus keeping chains of infection unbroken. We were optimistic, though the death rate was still approximately 80 per 100,000 and tuberculosis was still the leading cause of death.

We were optimistic even though the effects of the depression were observed on every hand. Despite unemployment in the cities, and drought and dust storms on the prairies, the thirties were not devoid of progress. There was greater realization by provincial and municipal governments that the costs of treatment of this long and treacherous illness were beyond the means of the individual to pay. The trend was steadily towards free treatment and the elimination of any means test in the treatment of tuberculosis.

Still another important development of the thirties was the expansion of the Indian and Northern Medical Services which led to the present excellent program. The way in which the "white plague" is being conquered among the Indians and Eskimos lifts a heavy burden from the conscience of other Canadians, and we will thankfully continue the program launched in the thirties.

It is interesting that in the closing years of a decade comes some ripple that swells to a tide in the next. The twenties were almost over when free treatment was inaugurated in one province. The thirties were nearly completed when amidst the preoccupations of World War II we heard important news from South America, the development of de Abreu's miniature x-ray, which was to revolutionize diagnosis.

We entered the forties in all the strain of war which has traditionally caused an increase in tuberculosis. And the increase came. So did staff shortages as nurses and doctors joined the services. Yet it was not all shadow, for the Dominion Government acceded to our request that all service personnel have chest radiographs taken so that tuberculosis would not be added to the other hazards confronting our fighting forces.

This program involved taking chest radiographs of a million Canadians of every economic, educational, geographic and occupational group. It showed that even among those who looked and felt healthy enough to present themselves for service, 1% had active tuberculosis.

This experience paved the way for a new program for local provincial associations to undertake mass chest radiographic surveys as soon as they could. Saskatchewan, pioneering again, laid down a pattern for community participation.

As soon as x-ray equipment was available at the end of the war, the mass surveys began. Unsuspected cases were found by the thousands. A building program became an urgent need, since every sanatorium had long waiting lists. As an example the building program in the province of Quebec can be cited. It doubled the treatment facilities in the province in ten years.

But the great breakthrough of the late forties was the discovery of streptomycin, the first really effective drug in the treatment of tuberculosis. Shortly thereafter, two other drugs were added and opened the way for the miracle of the fifties. In the next ten years the death rate was to fall faster than it had in the previous quarter of a century.

And so we face the sixties. What will they bring and what is our unfinished task? We realize that we have come a long way, but not far enough. We still have 9262 tuberculosis patients in hospital; 6500 new cases were found last year; 7256 were sent to hospital for the first time and there were 3500 readmissions. While the disease which Bunyan called the "Captain of the Men of Death" has lost its killing power, it is still a formidable enemy. It is still a disease which costs millions yearly and disrupts over 10,000 Canadian homes.

Perhaps our future work is more clearly outlined than we imagine; it is to press forward with our program of early diagnosis, treatment and education with all the energy we can.

There is some urgency as we face the future. Miracle drugs sometimes fail, resistance develops and it may be that the tubercle bacillus will do the same. The eminent epidemiologist, Dr. René Dubos of the Rockefeller Foundation, has voiced a warning that is a challenge to work harder than ever. He said recently that the curve of the epidemic of tuberculosis is at the bottom and that there is grave danger that it may start climbing again. Dr. Dubos thinks that we can eliminate tuberculosis, but he says "It's now or never; in 20 years it may be too late."

Our greatest challenge in the sixties will be an international one. Canada has been interested in the International Union Against Tuberculosis ever

since it was organized in 1920. During the past ten years we have been represented on the executive committee. In 1961 the Union will hold its next conference in Toronto. Not only will we be playing host to the representatives of 66 countries, but we will be largely responsible for organizing a conference program that it is hoped will provide practical answers to many tuberculosis problems throughout the world. None of us can feel fully content with our falling death rate when in a great part of the world tuberculosis is still the leading cause of death.

The 60th anniversary is a good time for us to face the fact that we are some distance from the conquest of tuberculosis in Canada and we have only made a beginning in the wide world.

MEDICO-LEGAL

MEDICAL MALPRACTICE LITIGATION—THE DOCTORS' DILEMMA*

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PART I OF FIVE PARTS

INTRODUCTION

THE CONCEPT that the medical practitioner is answerable for the unhappy results of his ministrations is shrouded in the mists of history. The ancient Babylonians, for example, however limited their knowledge of medicine may have been, held their doctors to severe accountability for any injurious effects of their services. The code of Hammurabi enacted in Babylon about 2030 B.C. provided that if a doctor treated a patient successfully for a severe wound the doctor was to receive ten shekels of silver. However, if the patient died, the doctor was to have his hands cut off.[1] While such severe provisions of the law may or may not have prevented medical malpractice, they undoubtedly reduced the indications for surgery in Babylon.

This extreme degree of legal liability of the ancient physician may strike the modern reader as amusing. However, today, forty centuries after the code of Hammurabi, the medical profession may have good reason to believe that the days of Babylon have returned. It is a fact that in both England and the United States the incidence of malpractice litigation has been increasing in recent years at an alarming rate. Similarly, the value of damages awarded has increased to near astronomical proportions.[2, 3] The result of these trends has posed the medical profession with a veritable doctors' dilemma compounded in great measure by the fact that it has been shown that in only a small percentage of cases is the doctor sued guilty of technical error.[4] The effect of the malpractice problem in terms of costs incurred in the course of litigation has been estimated at many millions of dollars. But this effect is relatively unimportant when one considers the far-reaching effect on the doctor-patient relationship and the day-to-day practice of medicine. With the threat of legal action hanging over his head like the sword of Damocles, the doctor today is placed in the invidious position in which he must minister to his patients with a reserve, caution, and circumspection which militates against the practice of the best medicine.

While it is true that the foregoing statement of the problem of malpractice litigation is based on the current situation in the United States, the problem is a real, serious, and growing one in Canada. The tidal wave of malpractice lawsuits and claims engulfing American courts has been reflected as a significant ripple in Canadian jurisdictions, and it is therefore submitted that the Canadian medical profession should become acutely aware of the inherent threat in current trends of malpractice litigation.[5] The principal objectives of this paper are therefore to inform medical practitioners of some of the principles of the law of malpractice, their origin and application; the extent of the present problem of malpractice; and the means whereby this problem might be solved. The timeliness and appropriateness of these objectives have been strongly emphasized by a notable expert on medical malpractice, in the following words:

> "An explanation of the basic rules of medical malpractice and their everyday application must be available to every practising physician, and if necessary must be emphasized over and over again, until the lesson is learned. An elementary exposition of the law of malpractice in plain English is an integral part of any worthwhile educational

*This paper was originally a thesis presented to the Faculty of Medicine, University of British Columbia, in partial fulfilment of the requirements for the degree of Doctor of Medicine. Sponsor: Dr. F. P. Patterson, M.D., F.R.C.S.[C], F.A.C.S.

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program. It should start in the medical schools. There should be a brief course taught in a realistic and elementary fashion in every medical school. The subject should be repeated to hospital residents by means of short lectures during the period of residency; the subject should again be repeated to all applicants for admission to county medical society membership. Sufficient time for at least an elementary discussion of malpractice should be allotted in each of these forums. In addition, seminars on medical malpractice should be conducted periodically by each county medical society."[6]

It is intended in this paper to examine some of the legal principles related to medical malpractice and to illustrate the application of these principles in court judgments. It is further intended to examine malpractice litigation as a current problem facing the medical profession, the reasons the problem exists, the effects it has had on medicine, and the means by which it might be solved.

The scope of this paper is necessarily beset by certain limitations. Firstly, the law of malpractice is a subject matter of great complexity and many ramifications. Secondly, the law varies from one jurisdiction to another. Furthermore, it is necessary to realize that the judgment in every malpractice action depends on the particular circumstances of its own case to which the general principles of law have been applied. It is not intended to submit a legal treatise but rather a general exposition limited to discussion of medical negligence, couched wherever possible in non-technical language, and illustrated wherever possible by English and Canadian legal decisions.

THE LEGAL BASIS OF MEDICAL MALPRACTICE LIABILITY

The Historical Evolution of Malpractice Liability

The historical evolution of medical malpractice liability can be traced to antiquity. Allusion has already been made to the penalties to which the improvident surgeon was exposed by the ancient code of Hammurabi. An examination of some of the sections of this code is illuminating. For example, it declared:

"215. If a doctor has treated a man for a severe wound with a bronze lancet, and has cured the man, or has opened an abscess of the eye for a gentleman with the bronze lancet and has cured the eye of the gentleman, he shall take ten shekels of silver.

"216. If he [the patient] be the son of a poor man, he shall take five shekels of silver.

"218. If the doctor has treated a gentleman for a severe wound with a lancet of bronze and has caused the gentleman to die, or has opened the abscess of the eye for a gentleman with the bronze lancet and has caused the loss of the gentleman's eye, we shall cut off his hands.

"219. If the doctor has treated the severe wound of a slave of a poor man with a bronze lancet and has caused his death, he shall render slave for slave."

From this brief quotation, several concepts of the Babylonian law appear. Firstly, the doctor was entitled to reward only if he effected a cure. Secondly, if he failed to cure but in the course of his services caused injury or death, he was subject to severe, retributary punishment. Thirdly, the doctor was apparently subject to punishment only for ill results which followed his positive acts, i.e. acts of commission. The concept that an act of omission, i.e. failure to act, could cause injury or death was too refined for the jurisprudence of that day. The sole test of liability seemed to lie in the fact of causation. Furthermore, it is interesting to notice that where the cure is effected on a patient who is poor in purse, the doctor's reward is less than when the patient is a gentleman. Similarly, if the doctor has caused the death of a slave, the punishment is merely a matter of compensation rather than amputation.

In ancient Egypt, general rules had been established for the treatment of patients and these rules were recorded in sacred books guarded by the priests.[1] As long as the physician conformed to these rules in his treatment, he was not liable for the results. However, if he departed from these rules and this departure resulted in the death of the patient, the physician was subject to beheading. Like the Babylonian law, the Egyptian law imposed a severe liability upon the physician but not an absolute one. Under the code of Hammurabi, the physician's responsibility was almost that of a guarantor and he acted at all times at his peril. The Egyptian law, however, represents a departure inasmuch as the physician could secure protection from this severe liability by conforming to the accepted, established standards. The sanction of law is therefore applied to the innovator or experimenter whose deviation from the well-trodden pathway has produced adverse results. This concept of law is a thread still visible in the fabric of modern legal doctrine.

The early Roman law contributed greatly to the evolution of the law of malpractice by introducing the concept of negligence as a criterion of legal liability.[1] Whereas Babylonian and Egyptian law established liability merely by the existence of a causative relationship between the act and the injury, Roman law measured legal responsibility in terms of fault or negligent conduct. The Romans distinguished "dolus" (malice) from "culpa" (fault or negligence), and an action against a doctor could be maintained on the latter alone. Such negligence could consist of a positive act or of a failure to act because of ignorance, lack of skill,

or failure to attend or care for a patient. This concept that negligence arose out of both acts of commission and omission, the "misfeasance" and "nonfeasance" of modern common law, represents an advance in legal thought, for, as seen earlier, the consideration that a causal relationship existed between an injury and a failure to act was foreign to the law of Babylon and Egypt. Furthermore, not only was negligence the basis of liability, but also there had to be a causal relationship between the act or omission complained of and the injury suffered. These concepts of early Roman law form the basis of the modern law of medical malpractice, namely, that no legal responsibility lies upon the physician for the ill results of his practice without proof of fault on his part.

The later Roman law as introduced into continental Europe around 1200 A.D. clarifies the concept of negligence as a test of liability and goes even further by stating a standard whereby negligence is measured.[1] Thus, the Roman law of this time provided:

> "Whoever employs the services of a person who makes a profession of the possession of an art or science, may, disregarding particular circumstances, pre-suppose that this person has such knowledge and abilities as one might acquire in such art or science by usual industry and conscientious application. There is no right to pre-suppose particular gifts or the endowment of genius."[1]

The standard of care which the public could rightfully expect from the medical practitioner was measured in the modern Roman law in terms of the care, knowledge, and skill which could be expected from the average practitioner and this is essentially the standard applied by the law today.

The English common law is not a direct descendant of the Roman law. Unlike the latter, it is not codified, but is composed of a body of judicial decisions recorded over the centuries and followed as precedents. Although not directly related to Roman law in form or substance, the English common law eventually came to adopt principles of malpractice liability similar to those provided by the Roman code.[1] The earliest recorded decision in England on the civil liability of a physician and surgeon dates back to the reign of Edward III in 1374.[7] In this case an action was brought against J. Mort, surgeon, arising out of the treatment of a wounded hand, the plaintiff claiming that because of the negligence of the surgeon, "the plaintiff's hand was so impaired that it was maimed to his injury and damage". Although J. Mort, surgeon, escaped liability on a technicality, the court clearly laid down the rule that if negligence is proved the law will provide a remedy. The court further stated that "If the surgeon does so well as he can and employs all his diligence to the cure, it is not right that he should be held culpable." A further historical recognition of medical malpractice is seen in the charter incorporating the College of Physicians of London in 1518.[7] This charter specifically empowered the College to discipline its own members for malpractice, the penalty provided being a fine of £60 or fourteen days' imprisonment.

A definitive expression of the civil liability of the medical practitioner in English law was voiced in 1534 by Sir Anthony Fitzherbert.[7, 8] In the legal writing of this jurist is found a suggestion that one may become liable to another for negligent conduct which constitutes no breach of contract. This bare hint of the principle which forms the legal basis of modern medical responsibility is contained in an oft-quoted passage which, interestingly, deals not with the action of a physician, but with the careless conduct of a blacksmith. The passage reads:

> "But if a smith prick my horse with a nail, I shall have my action upon the case against him without any warranty by the smith to do it well; and the writ shall be, wherefore he fixed a certain nail in the foot of a certain horse of J. at N. by which it became corrupted, so that the same horse for a long time could not labour, and he the said J. during that time lost the profit of his horse aforesaid, to the damage etc. For it is the duty of every artificer to exercise his art right and truly as he ought."[8]

The doctor of that day was considered to be an artificer practising a "common calling" like the apothecary, the barber, and the smith, and the duty imposed upon him as suggested by Fitzherbert originated from the mere exercise of the calling and not out of any contract between doctor and patient.[9] It has been suggested that this view of law follows upon the rudimentary conception of contractual liability of that day. Whether this is so or not, the principle that the law imposed a liability to the exercise of a calling represents a milestone in the evolution of our modern law of malpractice.

The cornerstone of modern malpractice liability in English common law may be said to be founded in the decision in 1615 of Sir Edward Coke in the case of Everard v. Hopkins.[8, 9] In that case, a master, having contracted with a surgeon for the care of his servant, claimed damages from the surgeon, alleging that the surgeon had been "careless" in his services and had administered "unwholesome medicines", to the injury of the servant. Sir Edward, the "father of the common law", rendered this decision:

> ". . . for this the master may have an action clearly; but the servant cannot have an action upon this agreement, but he may have an action upon the case for his applying of unwholesome medicines to him. . ."[8]

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The exact point of decision in this case is that a master who has contracted with a physician may recover damages for negligent administration of medicines to his servant. The judge's remarks regarding the rights of the servant were unessential to the decision of the point in issue. However, such seemingly extraneous statements may form the basis of future law and such was the case with the dictum of Sir Edward Coke. This dictum was expounded in later cases until it became the law that a servant, though a stranger to the contract between his master and the doctor, had an independent right to sue the physician if the latter was negligent towards the servant.

In the foregoing paragraphs, a brief survey of the historical origins of the legal liability of physicians has been attempted. It is seen that the concept of such liability dates from the most ancient days and in this modern era has evolved into a massive body of law, the general principles of which will be presently examined.

The Definition of Malpractice

Although the word "malpractice" has thus far been used quite freely, it would be well to give it some definition. In colloquial language, such definition might be stated as follows:

> "Malpractice is just another way of saying failure of a physician to use average skill, care, and precaution in rendering his professional services to a patient. The law of malpractice is a part of the over-all law governing human relations, which requires that all of us use reasonable care to avoid injuring others. It is a special part of the general law of negligence applicable to those who undertake to treat the sick and injured."[6]

The legal dictionary provides a more explicit and detailed definition of malpractice:

> "Any professional misconduct, unreasonable lack of skill or fidelity in professional or judiciary duties, evil practice or immoral conduct. As applied to physicians, in a more specific sense, it means bad, wrong, or injudicious treatment resulting in injury, unnecessary suffering, or death to the patient, and proceeding from ignorance, carelessness, want of proper professional skill, disregard of established rules or principles, neglect, or a malicious or criminal intent."[11]

A definition of malpractice incorporating more specifically statements of legal principles states:

> "Malpractice may be defined as the failure upon the part of a physician . . . properly to perform the duty which devolves upon him in his professional relation to his patient, a failure which results in some injury to the patient. The physician's duty arises as a matter of law out of the relation of physician-patient. This legal duty requires that the physician undertaking the care of a patient possess and exercise that reasonable and ordinary degree of learning, skill, and care commonly possessed and exercised by reputable physicians in the same locality, or in similar localities, in the care of similar cases; it requires also that the physician, in caring for the patient, exercise his best judgment at all times."[12]

The use of the word "malpractice" is itself unfortunate on two grounds.[6] Firstly, it carries with it the connotation that the doctor referred to is lacking in knowledge and skill. This is not true. The most learned, able and experienced doctor may in any given case be judged negligent by a court of law. Furthermore, malpractice in law is not restricted to physicians, but is applicable equally to lawyers, engineers, architects and other professional groups. Unhappily, however, the word conjures up the vision of the physician by its mere mention. It has been suggested that a more appropriate term would be "professional tort liability", but the word "malpractice" has been hallowed by usage in both medical and legal literature and would now be difficult to dislodge.

The General Legal Principles Applicable

The fundamental structure of the law in Canada is the common law of England unless altered or overruled by statutory enactments of the House of Commons or the provincial legislatures. It follows as a corollary, therefore, that the legal basis of malpractice liability is founded in the English common law.

But what is the common law? It is an uncodified body of law of diverse origins but primarily derived from the laws of Anglo-Saxon England and old English custom.[7, 13] It consists of an unbroken line of recorded judicial decisions dating from the end of the 12th century. These recorded decisions formed a body of precedents which were followed by the courts over the centuries and applied in the adjudication of new issues as they came before the courts. Two features of the common law are unique. Firstly, it is not a codified system of law as was the Roman law with its rigid structure of fixed, recorded rules. On the contrary, its principles were contained in the cases as decided with reference to the precedents set by earlier cases. For this reason, the common law is also called "case law" or "judge-made law". Rather than apply fixed principles to new conditions, it adapted itself to these conditions and evolved with time as a flexible, malleable instrument. The second unique feature of the common law is its adherence to the precedents established by previously decided cases. This adherence to precedence developed into a doctrine of common law known as "stare decises" which, stated simply, meant that the decision of

the higher courts has the force of law and is binding in all future cases.[7] By application of this doctrine, not only was the pathway of the law's evolution described, but also the continuity and predictability of its application was assured.

The general body of the common law has two main divisions, i.e. civil common law and criminal law. The distinction between a civil and a criminal wrong

> ". . . depends on the nature of the appropriate remedy provided by law. A civil wrong is one which gives rise to civil proceedings – proceedings, that is to say, which have as their purpose the enforcement of some right claimed by the plaintiff as against the defendant; for example, an action for recovery of a debt, or for the restitution of property, or for the specific performance of a contract, or for an injunction against a threatened injury, or for the recovery of damages for an injury committed. Criminal proceedings, on the other hand, are those which have for their object the punishment of the defendant for some act of which he is accused. He who proceeds civilly is a claimant, demanding the enforcement of some right vested in himself; he who proceeds criminally is an accuser demanding nothing for himself, but merely the punishment of the defendant for a wrong committed by him."[14]

In adjudicating issues of liability of physicians for malpractice, the doctrines of the civil common law are applied. These doctrines fall into two main categories, namely, the law of contract and the law of torts. Although both of these classes of civil law affect the legal responsibility of a physician, the basis of this responsibility lies essentially in the law of torts. The law of contract does create the physician-patient relationship and can modify the scope of the doctor's duty which arises automatically, as will be seen, under the law of tort. However, the dimensions of malpractice liability are described by the law of torts. But what is the law of torts? It is a body of legal principles which permit a person to recover damages by way of compensation for injuries due to the invasion of his rights of property or personality by another in the absence of contractual relationships.[13] The term "tort" eludes ready definition and legal minds have long grappled with its subtleties. It is a generic term which embraces a group of civil wrongs and may be defined as follows:

> "In general, a tort consists in some act done by the defendant whereby he has without just cause or excuse caused some form of harm to the plaintiff."[15]

A more specific definition states that a tort is:

> "A civil wrong for which the remedy is a common law action for unliquidated (i.e. unspecified) damages, and which is not exclusively the breach of a contract or the breach of a trust or other merely equitable obligation."[15]

Some of the civil wrongs known as torts are: assault, fraud, libel, false imprisonment, and negligence, and the physician may commit and be sued for any of these by his patient.[13] For example, the tort of assault consists of the touching of another for which no consent has been obtained. Therefore, the surgeon who, with permission to remove the appendix, also removes the tonsils, may be sued for assault. Again, the physician may be liable for fraud if he induces a patient to continue a worthless therapy merely to derive fees. Furthermore, the tort of false imprisonment, i.e. the holding of another against his free will, may be committed by a physician who detains or commits a patient of sound mind. However, these cited examples form exceptional instances of medical malpractice. The broad basis of malpractice liability is founded on the proof of the tort which is called negligence. It is the tort of negligence with which the doctor is principally concerned because almost invariably an action against a doctor for malpractice is an action alleging the commission of that specific tort.[16, 17]

Much has been said in the English decisions about what constitutes negligence. The oft-quoted definition given by the jurist Baron Alderson phrases it in these words:

> "Negligence is the omission to do something which a reasonable man, guided upon those considerations which ordinarily regulate the conduct of human affairs, would do, or doing something which a prudent and reasonable man would not do."[18]

However, the concept of negligence is more complex than this statement taken alone would suggest. The foregoing definition is merely a general expression of the nature of the conduct which is basic to the establishment of negligence. But negligent conduct alone is not sufficient to establish negligence in law. In the words of Lord Wright:

> "In strict legal analysis, negligence means more than heedless or careless conduct, whether in omission or commission: it properly connotes the complex concept of duty, breach and damage thereby suffered by the person to whom the duty was owing."[19]

It follows, therefore, that for the legal wrong of negligence to exist there must first exist a duty of care owing by one person to another, there must be a failure of compliance with this duty of care, and damages must have resulted to the person to whom the duty is owed. The principle of a duty of care is unique to English law. It is absent in Roman law which imposed liability as long as damage was done unjustifiably, irrespective of any relationship between the parties.[21] But the duty of care imposed by English law is not universal, it does

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not exist at all times nor does it extend to all persons. Whether there is a duty of care in any particular circumstances is a question of law. The general statement of principle upon the question of the duty of care is well established as stated by Lord Atkin:

> ". . . The rule that you are to love your neighbour becomes in law, you must not injure your neighbour; and the lawyer's question, 'who is my neighbour?' receives a restricted reply. You must take reasonable care to avoid acts or omissions which you can reasonably foresee would be likely to injure your neighbour. Who then, in law, is my neighbour? The answer seems to be – persons who are so closely and directly affected by my act that I ought reasonably to have them in contemplation as being so affected when I am directing my mind to the acts or omissions which are called in question."[20]

The law must go beyond merely enunciating the rule that a duty of care is owed by one person to another. Care is a relative matter, and it is necessary to define what standard of care the law requires to discharge the duty it imposes. Again, whether the legal standard of care is met is a question of fact in each particular case. However, in determining this question, two factors must be considered, namely, the magnitude of the risk to which others are exposed, and the importance of the object of the conduct in question. Thus, if a certain act carries with it great risk as measured by the likelihood and seriousness of injury, then the standard of care demanded in such case is commensurately higher. Similarly, if the act with attendant risk attached is performed with a view to achieving an important objective, the conduct will be considered as reasonable as the objective is important. Generally speaking, the standard of care is usually expressed in terms of the conduct of the "reasonable man" and it is the conduct of this hypothetical person which is used as a yardstick. As stated by Lord Macmillan:

> "The standard of foresight of the reasonable man eliminates the personal equation and is independent of the idiosyncracies of the particular person whose conduct is in question. Some persons are by nature unduly timorous and imagine every path beset with lions; others, of more robust temperament, fail to foresee or nonchalantly disregard even the most obvious dangers. The reasonable man is presumed to be free from over-apprehension and from over-confidence."[22]

A simple but frequently occurring example of an action based on the tort of negligence is that arising out of injuries sustained in motor vehicle accidents. If A operates a motor vehicle with a lack of care or skill, e.g. by speeding in traffic, so that B as a result suffers injury, B is entitled to recover damages from A. The law declares that A owes a duty of care to B, provided B is a person who might reasonably be contemplated to be affected by A's lack of care and skill, i.e. where B is, for example, a passenger in another vehicle or a pedestrian. The duty imposed on A is to operate his vehicle with the care and skill one might expect from a reasonable man. Failure of A to meet this standard renders him liable in damages for the tort of negligence.

MEN AND BOOKS

FELLOWSHIP OF SURGEONS

R. I. HARRIS, M.B., F.R.C.S.[C], *Toronto*

UNDER this title, Loyal Davis' book recently published by Charles C Thomas, Springfield, Ill., records the founding in 1912 of the American College of Surgeons and its growth and development, despite many vicissitudes, through the ensuing 48 years. From its earliest years the College displayed a vigour which ensured its survival and enabled it to maintain its high purpose and successfully accomplish its programs for the advancement of surgery by the education of American surgeons by annual clinical congresses, the elevation of hospital standards, the encouragement of graduate training of surgeons and the abolition of fee splitting and other unethical practices.

This history of the American College of Surgeons is intimately associated with the name of Franklin Martin, for it was he who conceived the idea of establishing an organization dedicated to the principle of attaining a high standard in the practice of surgery in the United States and Canada. He was a man of remarkable qualities who practised surgery and gynecology in Chicago. As a young man he saw the need for surgeons to exchange ideas and experiences in order that they might keep themselves continuously abreast of the advances in surgery which at the time was expanding at an explosive rate under the stimulus of Lister's revolutionary discoveries. As a first step towards the attainment of this ideal, he and his wife and a few of his surgical confreres contributed $24,000 to found the Surgical Publishing Company of Chicago, which in 1905 commenced publication of *Surgery, Gynecology*

and Obstetrics, a journal dedicated to the presentation of original articles on surgery and abstracts of all important articles from local and foreign journals.

Surgery, Gynecology and Obstetrics was a success from its inception and in a few years was financially secure. In 1910 Franklin Martin, managing editor of *Surgery, Gynecology and Obstetrics*, organized a clinical meeting of two weeks' duration which was held in Chicago, November 7 to 19. All the expenses involved in the organization of this meeting were paid from the treasury of *Surgery, Gynecology and Obstetrics*. This experiment in postgraduate instruction of surgeons was an unqualified success; 1300 surgeons attended the operating theatres of the leading Chicago surgeons and were enthusiastic about the opportunities which this Congress provided for them to see great surgeons at work and to exchange ideas with their fellow surgeons from all parts of the United States and Canada. Before the meeting ended, the assembled surgeons founded the Clinical Congress of Surgeons of North America to ensure that such meetings would be continued annually.

The second clinical congress was held in Philadelphia in 1911 and the third in New York in 1912. Both attracted large numbers of doctors. Only a few had the advantage of the best training available in that day; most had qualified by training under a preceptor, some were qualified only by their own experience and many were ambitious to learn enough by watching famous surgeons at work to be able to perform the surgery in their own general practices.

It was on his way to the New York Congress of 1912 that Franklin Martin conceived his plan for a "College of Surgeons of the United States and Canada" which would be limited to those practising surgery after adequate training, whose qualifications would be recognized by admission to Fellowship in the College. Before the clinical congress in New York ended, it adopted a resolution "to assume the responsibility and the authority of standardizing surgery". This led immediately to the incorporation of the American College of Surgeons (November 25, 1912).

In the years which have followed, the American College of Surgeons has wielded a great and increasing influence upon the surgical world of North America. Its path has not always been smooth. The administrative organization imposed upon it by Franklin Martin's strong leaning to the Democratic party's principle of States Rights gave ill-defined powers to a Board of Governors made up of appointees from each state of the United States of America and each province of Canada. The Board of Regents, the governing body of the College, was supposed to be appointed by the Board of Governors, but in actual practice for many years the Board of Regents submitted a slate of new Regents to the Board of Governors, who approved of the appointments without discussion. This gave the Board of Regents the appearance of being a self-perpetuating body. Much criticism arose from this and led finally to revision of the by-laws, enlarging and clarifying the powers of the Board of Governors. This has increased the powers of the states and provinces in a national College which should receive its support directly from its Fellows without any intermediary state or provincial organization. The American Medical Association for many years was critical of the American College, and perhaps still is. Instead of co-operation between the two bodies, there was obstruction and bickering. Also many personal feuds marred the early years of the history of the College.

In spite of these difficulties the American College has major accomplishments to its credit. It has been a great force in improving the standard of surgery in the U.S.A. and, to a lesser degree, in Canada. The standardization of hospitals has been one of its most significant achievements. For many years the College bore the responsibility and the expense of this program alone. The great improvements resulting from this activity in the quality of hospital service to the public were finally recognized by the American Medical Association, which now has joined with the College, the American Hospital Association and the American College of Physicians in the continuation of this program. For some time the Canadian Medical Association also shared in this program of hospital standardization. The College has greatly broadened and improved the programs of resident training of surgeons. In the early days there was scarcely any formal training of surgeons even in medical schools. Almost all training was by preceptorship. Largely through the influence of the College, formal courses of resident training have been established in several hundred hospitals approved for this purpose by the College. Many are hospitals not associated with medical schools. The College influenced the study of cancer. Its first activity in this field was the establishment of the Registry of Bone Sarcoma, the child of Codman's fertile brain. The college has fought a long and bitter battle against fee splitting and other unethical practices. While this battle is not yet won, the College has made great progress and has clarified and improved the situation enormously.

In one field the College did not succeed. The incorporation of qualifying Boards for all the different departments of medicine and surgery by the Council on Medical Education and Hospitals of the American Medical Association deprived the College of the power to assess the training and experience of aspiring surgeons and to subject them to the examination necessary to determine their qualifications to practise surgery.

For several reasons this volume has important interest to Canadians. In the first instance several prominent Canadians were amongst the founding fellows, among them W. W. Chipman of Montreal (who was president in 1924), H. A. Bruce, Sterling Ryerson and Frederick Marlow of Toronto and Robert E. McKechnie of Vancouver. Canadians also played an important part in the successful development of the various programs which the College initiated. In 1923 Malcolm MacEachern of Vancouver was engaged to conduct the program of hospital standardization and development. He continued to assume this responsibility for 27 years and became Director of the College in 1949. Beaumont Crowell was Assistant Director in charge of the Registry of Bone Sarcoma where he pioneered in the guidance of studies in the results of treatment of malignancies. But the most important feature of this volume for Canadians is the lesson we can learn of the principles which should guide a national college of surgeons if it is to avoid the serious problems with which the American College has struggled, in order that our College may wield the greatest influence for the progress of surgery in Canada with the minimum of administrative difficulties.

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CASE REPORTS

RECURRENT EPISODIC BLINDNESS IN CRANIAL ARTERITIS

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CRANIAL ARTERITIS (temporal arteritis, giant-cell arteritis) is generally considered a rare disease. Awareness of this disease syndrome is the most important factor in the establishment of the diagnosis. Suspicion should be aroused in the case of any middle-aged (or older) patient with headache of recent onset, especially when an associated high erythrocyte sedimentation rate is found.

Because of the possibility of serious visual complications, varying from transitory amblyopia to complete blindness, it is vitally important to suspect this disease and institute treatment without delay. It is considered that corticosteroids and anticoagulant therapy combined may prevent the occurrence and/or progression of the visual complications.[1]

The following features were manifested by a patient with this disease, recently treated by the authors. Over a period of 11 days in hospital he lost his vision completely on 46 occasions. These episodes of amaurosis fugax (temporary blindness) lasted from 5 to 15 minutes. Both eyes were involved on different occasions, the left 38 times and the right eight times. In view of the favourable circumstances for observation of this patient and because of the unusual manifestations of his disease, it is felt that this case warrants reporting.

T.N., a 72-year-old Ukrainian man, was admitted to St. Boniface Hospital on February 14, 1959, for investigation of headache. His past history revealed no serious illnesses. His main complaint was of a severe, steady right frontal and occipital headache that started during the first week of November 1958. The onset was accompanied by nasal stuffiness and watery eyes for three to four days. The "head-cold" cleared without treatment, but the constant headache remained, unrelieved by analgesics. In early February of 1959, he again developed a "head-cold" comparable to the previous one. The headache which was still present became much more severe, and, as before, was unaffected by analgesics. He was seen by an ophthalmo-otolaryngologist who referred him to a neurosurgeon upon observing choked discs on funduscopic examination. Subsequently the patient was admitted to hospital for further investigation.

On admission, his temperature was 99.3° F., and he looked pale and exhausted. There was no history of dizziness, fainting spells, tinnitus, or behavioural and memory changes. He stated that his left eye was weaker than the right, and his appetite had been very poor for the last two to three weeks. Pertinent physical findings were as follows: The pupils were equal and reacted to light. There was no evidence of papilledema. Blood pressure was 105/65 mm. Hg. Pulse rate was 84 per minute. Neurological examination was essentially negative.

On admission the hemoglobin value was 13.0 g. %; erythrocyte sedimentation rate 107 mm./hour (Westergren); hematocrit 38%; white blood cell count 13,500/c.mm. with a differential count of 76% mature neutrophils, 10% band neutrophils, 9% lymphocytes, 4% monocytes and 1% disintegrated cell. Urine was normal. Skull radiographs were non-contributory and radiographs of the paranasal sinuses were normal. Bilateral cerebral angiograms taken on February 16, 1959, revealed no evidence of distortion or displacement of the cerebral vessels. Both internal carotid arteries were patent.

On February 17, 1959, the day after angiography, he was examined by an ophthalmologist. The findings were recorded as follows: visual acuity, right 20/40, left 20/30; pupils, right 3 mm., reacted to light and left 3 mm., did not react to light; tension in both eyes, 23 mm. Hg; fundi—discs flat, arteries arteriosclerotic 2+, veins full 2+. During the examination, the patient suddenly exclaimed: "My sight has gone in my left eye." Immediate funduscopic examination of that eye revealed a spasm of the central retinal artery, with almost complete disappearance of the retinal branches. The retinal veins became much attenuated, and segments became invisible in the retinal edema. There were no hemorrhages. In a few minutes the retinal

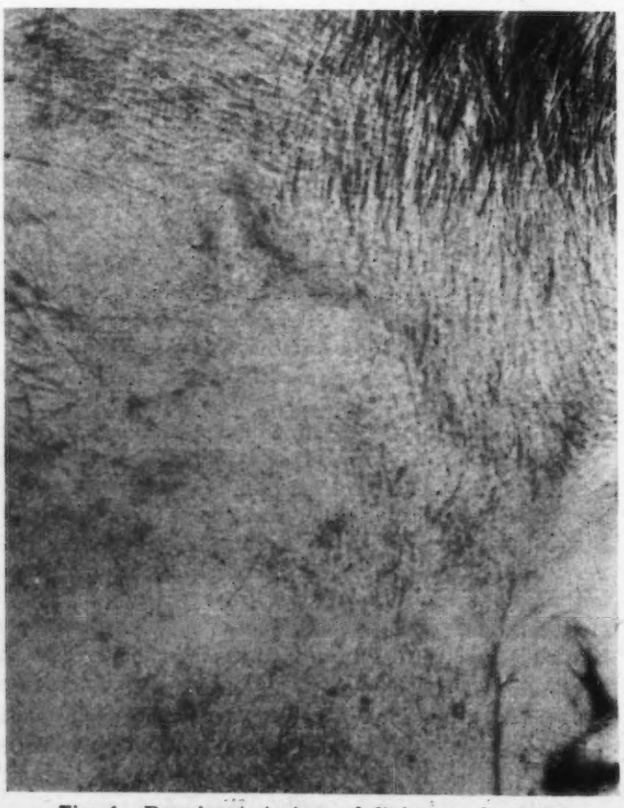

Fig. 1.—Prominent, tortuous left temporal artery.

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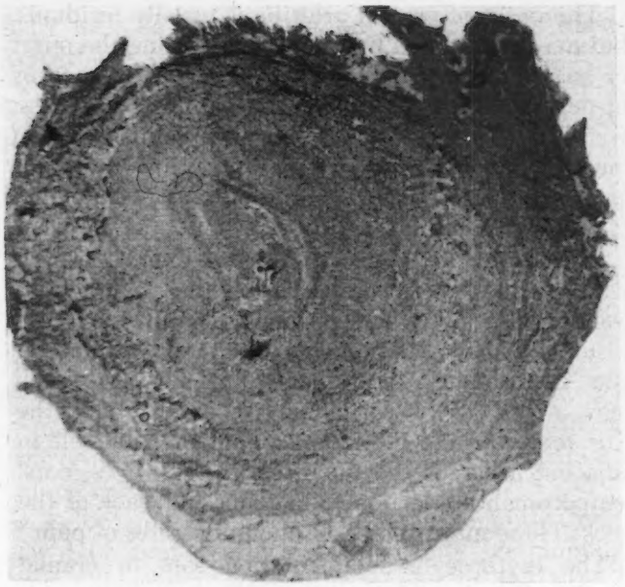

Fig. 2.—Low-power view of cross-section of right temporal artery, showing intimal proliferation with fibrosis and marked inflammatory response.

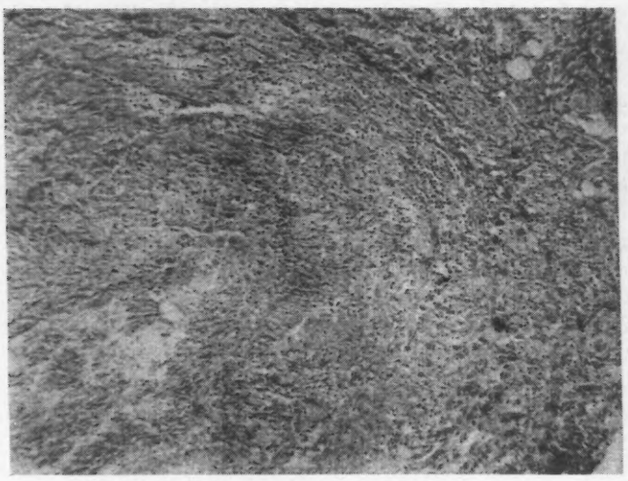

Fig. 3.—High-power view, showing fibrosis, fragmentation of elastic laminae, and inflammatory response with presence of multinucleated giant cells.

picture returned to normal and his vision returned. Both temporal arteries were noted to be prominent, tortuous and tender (Fig. 1). Both arteries were pulsatile.

With a provisional clinical diagnosis of cranial arteritis, cortisone therapy was commenced immediately. At the time when cortisone was started, the temperature was 101° F. Next morning the patient woke with complete relief of his headache. His temperature was 96.7° F. Anticoagulant therapy was begun at the same time.

A biopsy of the right temporal artery performed on February 18 revealed that this artery had a pin-sized lumen. The intimal layer was swollen and the elastic fibres were destroyed, with increased fibrosis and multinucleated giant cells (Fig. 2). Throughout all layers of the arterial wall there were numerous lymphocytes and polymorphonuclear leukocytes (Fig. 3). The pathological diagnosis was temporal arteritis. Bacteriological culture of a segment of the artery revealed no growth apart from saprophytic staphylococci (probably from skin contamination).

Other laboratory results were: prothrombin time 33%; serum protein value 6.6 g. %; albumin 2.15 g. %, α_1 globulin 0.62 g. %, α_2 globulin 1.39 g. %, β globulin 0.83 g. % and γ globulin 1.59 g. %; C-reactive protein value 6+; and L.E. cell test negative. Skin temperature studies showed no gross abnormality.

Blood pressure recordings before, during and after attacks of blindness did not vary. Tonometric readings remained equal throughout. Before attacks of visual loss, the patient frequently experienced scintillations of silver, blue and red lights. On many occasions the central retinal artery of the involved eye was found to be in spasm, with blanching of the retinal branches. The retinal veins were seen to be engorged, with the column of blood segmented in clumps like a box-car formation. No hemorrhages or exudates were seen on the funduscopic examination at any time.

The course of treatment is outlined in Table I. By February 22, five days after the institution of cortisone

TABLE I.

Hospital days	*No. of attacks of blindness*		*Temperature*	*E.S.R.*	*Medications*									
	Left eye	*Right eye*			*Codeine*	*Erythromycin*	*Chloramphenicol*	*Amyl nitrite*	*Cortisone*	*Heparin*	*Pentaerythritol tetranitrate*	*Bishydroxycoumarin*	*Tolazoline*	*Nitroglycerine*
1	0	0	100.3*		×									
2	0	0	101.2		×	×	×							
3	0	0	101.4		×	×	×	×	×	×				
4	6	0	101.0	107†	×	×	×	×	×	×	×	×		
5	4	0	98.1	62		×	×	×	×	×	×	×		
6	6	2	98.6	107		×	×	×	×	×	×	×	×	
7	9	3	97.4					×	×	×	×	×	×	×
8	7	0	96.8	104				×	×		×	×	×	×
9	2	2	98.0					×	×		×	×	×	×
10	1	0	97.6						×		×	×	×	×
11	2	0	97.6						×		×	×	×	×
12	1	0	98.6						×		×	×	×	
13	0	0	98.0						×		×	×	×	
14	0	0	98.0						×			×	×	
15	0	1	97.8						×			×	×	
16	0	0	98.0						×			×	×	
17	0	0	98.4						×			×	×	
18	0	0	98.0						×			×		
19	0	0	98.2	93					×			×		
20	0	0	98.0						×					
21	0	0	98.8						×					
22	0	0	99.0						×					
23	0	0	98.6						×					
24	0	0	98.0						×					
25	0	0	98.0						×					
26	0	0	98.2						×					
27	0	0	96.6						×					

*Temperature in °F. (highest recording of the day).
†Erythrocyte sedimentation rate in mm. in one hour (Westergren).

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therapy, the temporal arteries were markedly reduced in size and definitely softer. Anticoagulants were discontinued on March 4, four days after the last attack of amblyopia. Cortisone was continued and he was sent home on March 12, 1959, in good condition, with no recurrence of headache or visual loss, on a maintenance dose of 75 mg. cortisone daily.

This patient was seen at intervals from one to two months. By September 4, 1959, his erythrocyte sedimentation rate was 10 mm. in one hour (Westergren). Cortisone was discontinued at this time. On October 22, 1959, the erythrocyte sedimentation rate remained the same. However, when it rose to 48 mm. in one hour in November 1959, further cortisone therapy was instituted. Since then he has been maintained at a dosage of 37.5 mg. per day, without recurrence of symptoms.

DISCUSSION

The term "temporal arteritis" was first suggested by Horton *et al.* in 1932.[2] The clinical picture was first described by Jonathan Hutchinson in 1890.[3] Schmidt[4] in 1931 described a case in an elderly man who subsequently developed visual complications. In 1940 Sprague and Mackenzie[5] introduced the term "Horton-Magath syndrome" to describe this disorder. Gilmour[6] suggested the term "giant-cell chronic arteritis", while Kilbourne and Wolff[7] recommended "cranial arteritis" because of possible involvement of cerebral, renal and ophthalmic arteries, and other branches of the carotid artery.

The etiology of this disease is still obscure. It usually affects persons 55 years of age and over. Most are over 65 years of age. Rarely, young people in their twenties may be affected.[8, 9] There is no predilection for either sex,[10] although earlier reports showed a higher incidence in women.[7] Reported cases are almost always in whites.[11]

The clinical and histological features suggest an infectious process, but there is no convincing proof. Various organisms had been isolated with no constant bacterial findings.[2, 12] Those who believe in the infectious nature of this process have postulated that contiguous spread of infection takes place along the branches of the external carotid artery, arising from infections in the mouth, teeth and sinuses.[7] Allergy has been considered as the etiological factor also, with vascular changes of the nature of an allergic angiitis.[13] Generally, cranial arteritis is regarded as a collagen disease, but usually is considered distinct from periarteritis nodosa.[14]

The disease affects all layers of the arterial wall. There is intimal proliferation, fragmentation of elastic laminae, medial necrosis with replacement by granulation tissue and infiltration by lymphocytes, plasma cells and foreign-body giant cells. The affected artery becomes tortuous and swollen, and may clinically appear as nodular lesions or as a solid cord. Besides the temporal artery, the occipital, facial, ophthalmic, central retinal, ciliary and maxillary arteries may be involved.[7, 11]

The onset of cranial arteritis is usually insidious, but may be sudden. Frequently preceding the onset of headache, there is a period of weeks or months of general malaise, anorexia, fatigability, weakness, weight loss, night sweats, dizziness, vague pains in muscles and joints, dyspepsia, and a low fever not associated with chills. A mild normocytic anemia may be present.

The headache is usually severe and constant, with associated hyperalgesia of the scalp. It is usually throbbing and boring in nature, but occasionally sharp. It may be unilateral or bilateral and is frequently aggravated by jaw and neck movements.[10, 15] Wearing a hat or combing the hair may become intolerable. Pain may be felt in adjacent areas of the face, teeth, jaws, eyes, ears, temporomandibular joints, zygoma and back of the neck. These may, in fact, be the initial sites of pain.[7]

The erythrocyte sedimentation rate in cranial arteritis is invariably increased, frequently exceeding 100 mm. in one hour (Westergren).[11] There is usually a mild to moderate leukocytosis, with a preponderance of polymorphonuclear neutrophils.

Ocular complications occur in at least 40% of cases according to Schick and Kvale.[11] Wagener and Hollenhorst[16] estimate the frequency of such changes at 56%. Bruce[17] in reviewing the literature found that 38% of patients had blindness of both eyes; 27%, blindness of one eye; and 20%, various degrees of impairment of vision. Whitfield *et al.*[18] reported 16 patients with ocular involvement out of a series of 31 cases; of these, eight became totally and permanently blind.

Ocular palsy, if it occurs, usually occurs after the onset of headache. This may be transient and may precede the onset of blindness.[19] As a result of the occlusive process involving the ophthalmic or central retinal artery or perhaps the central artery of the optic nerve, the commonest complaint is that of a misty brown veil, black cloud, "smoke screen" or "blind" over part or whole of the eye, which comes on suddenly, often first noticed on awakening.[10, 12, 20] The loss of vision may be sudden in one or both eyes.

In a series of 122 patients, Wagener and Hollenhorst found 68 with ocular involvement, of whom 20 experienced amaurosis fugax (fleeting blindness). Of these, 16 became permanently blind. The commonest cause of the visual loss was ischemic optic neuritis. Papilledema was present in 59 of the 64 eyes affected by ischemic optic neuritis. Small hemorrhages or, more frequently, "cotton-wool" patches were associated with papilledema. In the early stages, fragmentation of the blood stream was commonly seen in one or more of the retinal arteries or veins. Cardell and Hanley[9] noticed severe spasm in the retinal arterioles. Cooke *et al.*[21] postulated that in those cases where the ischemic process is temporary as a result of temporary swelling of the vessel wall of the arteries supplying the optic and oculomotor nerves (and probably the retina too), restoration of function may occur. This

may well be the explanation for amaurosis fugax in certain cases of cranial arteritis.

Signs of cerebral damage and encephalitis may be present during the acute stage of the illness. Mental changes, dulling of intellect, dysarthria, delirium and even coma have been reported.[5, 7] Whitfield *et al.*[18] found that coronary or cerebral thrombosis was the cause of death in most patients afflicted with cranial arteritis which terminated fatally. This raises the questionable role of cranial arteritis as part of a more widely generalized arteritis.

Cranial arteritis is a self-limited disease which runs its course within a period of two months to thirty months. Relapses may occur.[11] Most patients may expect eventual recovery.

Before the introduction of corticosteroids, treatment of cranial arteritis was mainly symptomatic and supportive, consisting mainly in the use of analgesics for the relief of pain. Local injection of procaine hydrochloride along the course of the involved artery may bring relief. Local radiotherapy may also be of symptomatic benefit. Excision of the involved segment of the temporal artery frequently brings about dramatic relief of pain. Shannon and Solomon[22] considered that the relief obtained from excision of the involved segment of the artery may be due to an interruption of the sympathetic fibres in the temporal artery. This minor procedure also furnishes material for a definite pathological diagnosis. Shick and Kvale found antibiotics and sulfonamides of no value in the treatment of this disease.[11] Massage of the ocular globes along with inhalation of amyl nitrite may relieve the prodromal visual symptoms.[23] Birkhead *et al.*[1] reported that intermittent inhalation of 100% oxygen seemed to be of some benefit in those with acute or recent visual impairment. They were not impressed with the value of vasodilating drugs or stellate ganglion blocks.

Since the advent of the adrenal corticosteroids and their introduction in the treatment of temporal arteritis by Shick *et al.*,[24] a new horizon has been reached. Prompt and dramatic subjective relief of both local and systemic symptoms are obtainable by this means, along with reduction of both fever and the erythrocyte sedimentation rate. Birkhead *et al.* emphasized the value of cortisone and related adrenal corticosteroids in the prevention and treatment of temporal arteritis and particularly of its most serious complication, blindness. They recommended that cortisone therapy be started as soon as the diagnosis is suspected, without any delay. Whitfield and his associates believe that cortisone therapy is unlikely to improve the vision of those with total blindness or long-standing partial loss of vision. If the loss of vision is partial or recent, some amelioration may be expected, but normal sight is unlikely to return. Although symptoms and objective evidence of active disease disappear with the use of corticosteroids, the erythrocyte sedimentation rate may remain high for weeks or months. As long as this finding is present, vision is constantly threatened, and maintenance doses of corticosteroids are required until the disease has run its natural course. Parsons-Smith,[25] in reviewing 50 consecutive patients with temporal arteritis seen at the Western Ophthalmic Hospital (St. Mary's Hospital), London, over a period of five years, reported that ACTH given on the same day as the blindness had restored sight in every eye so treated. He and others believe in the concurrent use of anticoagulants with corticosteroids to prevent possible intravascular thrombosis in the affected artery.[1, 23, 25]

The diagnosis of temporal arteritis in this case was confirmed by pathological examination. The role of angiography and its relation to the multiple episodes of loss of vision is uncertain. No episodes of amaurosis fugax occurred before angiography, but there were 46 such episodes after this procedure, 38 times in the left eye and 8 times in the right eye. Perhaps the central retinal vessels were more easily put into a state of spasm owing to the contrast media injected. This is conjecture only. It is interesting to note that this patient complained of seeing scintillations of coloured lights at the onset of an attack of blindness on several occasions. These photopsiae have been reported to occur in temporal arteritis.[14] On many occasions, spasm of the retinal branches was observed during an attack of blindness. The retinal veins became engorged and fragmented into segments, resembling a box-car formation. These findings too have been observed by others.[9, 10, 12, 20] Amyl nitrite did not abort attacks of visual loss. Antibiotics failed to lower the temperature in this patient, but cortisone brought about dramatic relief of the headache and reduction of the temperature to normal. In the first 24 hours the patient received 300 mg. of cortisone. Both temporal arteries were definitely softer and reduced in size five days after the institution of cortisone therapy. However, amaurosis fugax continued for 11 days after the start of corticosteroid and anticoagulant therapy. According to Hollenhorst,[26] amaurosis fugax in cranial arteritis does not as a rule continue once corticosteroid therapy has been commenced. In the Mayo Clinic series, only one of 170 patients (up to March 23, 1959) continued to have amaurosis fugax for almost ten days. It was believed that she received too low a dosage of cortisone and that it was tapered off too rapidly. In the present case, the patient received 300 mg. of cortisone the first day, tapered to 225 mg. daily four days after the first attack of blindness. By March 6, 1959, he was receiving a daily dose of 100 mg., and by March 11, 87.5 mg. He was discharged on March 12, on a maintenance dose of 75 mg. of cortisone daily. During his hospital stay he received a total dosage of 3950 mg. of cortisone. At this writing he is receiving a daily dose of 37.5 mg. with no recurrence of headache or attacks of visual loss, but in February 1960 this patient developed acute glaucoma in his right eye.

SUMMARY

A case of recurrent episodic blindness associated with cranial arteritis is reported. Amaurosis fugax occurred 46 times, 38 times in the left eye and 8 in the right eye.

The literature on this disease syndrome is reviewed, with particular emphasis on the ocular complications.

The possibility of cranial arteritis must be suspected in any patient over 55 years of age with headache of recent onset and an associated high erythrocyte sedimentation rate.

Prompt corticosteroid therapy is essential in all suspected cases of cranial arteritis to bring about relief of local and systemic symptoms, and of most importance to prevent ocular complications and to safeguard vision. The concurrent use of anticoagulants with corticosteroids is recommended in those with ocular involvement.

We would like to thank Dr. M. Van Wijhe, Pathologist, St. Boniface Hospital, St. Boniface, Manitoba, for the preparation and selection of the microscopic slides, and Mr. L. V. Stanford, Department of Art and Photography of the hospital, for the photographic preparations.

REFERENCES

1. BIRKHEAD, N. C., WAGENER, H. P. AND SHICK, R. M.: *J. A. M. A.*, **163**: 821, 1957.
2. HORTON, B. T., MAGATH, T. B. AND BROWN, G. E.: *Proc. Staff Meet. Mayo Clin.*, **7**: 700, 1932.
3. HUTCHINSON, J.: *Arch. Surg.* (Lond.), **1**: 323, 1890.
4. SCHMIDT, M.: *Brain*, **53**: 489, 1931.
5. SPRAGUE, P. H. AND MACKENZIE, W. C.: *Canad. M. A. J.*, **43**: 562, 1940.
6. GILMOUR, J. R.: *J. Path. & Bact.*, **53**: 263, 1941.
7. KILBOURNE, E. D. AND WOLFF, H. G.: *Ann. Int. Med.*, **24**: 1, 1946.
8. MEYERS, L. AND LORD, J. W., JR.: *J. A. M. A.*, **136**: 169, 1948.
9. CARDELL, B. S. AND HANLEY, T.: *J. Path. & Bact.*, **63**: 587, 1951.
10. RUSSELL, R. W. R.: *Quart. J. Med.*, **28**: 471, 1959.
11. ALLEN, E. V., BARKER, N. W. AND HINES, E. A., JR.: Peripheral vascular diseases, W. B. Saunders Company, Philadelphia, 2nd ed., 1955, p. 346.
12. CROSBY, R. C. AND WADSWORTH, R. C.: *Arch. Int. Med.*, **81**: 431, 1948.
13. MCCOMBS, R. P., PATTERSON, J. F. AND MACMAHON, H. E.: *New England J. Med.*, **255**: 251, 1956.
14. CAMERON, A.: *Brit. M. J.*, **2**: 1291, 1959.
15. CHASNOFF, J. AND VORZIMER, J. J.: *Ann. Int. Med.*, **20**: 327, 1944.
16. WAGENER, H. P. AND HOLLENHORST, R. W.: *Am. J. Ophth.*, **45**: 617, 1958.
17. BRUCE, G. M.: *Ibid.*, **33**: 1568, 1950.
18. WHITFIELD, A. G. W. *et al.*: *Lancet*, **1**: 408, 1953.
19. MEADOWS, S. P.: *Tr. Ophth. Soc. U. Kingdom*, **74**: 13, 1954.
20. CACCAMISE, W. C.: *Am. J. Ophth.*, **42**: 779, 1956.
21. COOKE, W. T. *et al.*: *Quart. J. Med.*, **15**: 47, 1946.
22. SHANNON, E. W. AND SOLOMON, J.: *J. A. M. A.*, **127**: 647, 1945.
23. PARSONS-SMITH, G.: *Brit. J. Ophth.*, **36**: 615, 1952.
24. SHICK, R. M., BAGGENSTOSS, A. H. AND POLLEY, H. F.: *Proc. Staff Meet. Mayo Clin.*, **25**: 135, 1950 (abstract).
25. PARSONS-SMITH, G.: *Brit. J. Ophth.*, **43**: 204, 1959.
26. HOLLENHORST, R. W.: Personal communication, March 23, 1959.

ACUTE HEMOLYTIC ANEMIA DURING SULFONAMIDE THERAPY

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ACUTE HEMOLYTIC episodes during the use of various sulfonamides were first described by Harvey and Janeway[1] in 1937. Since then numerous examples of this type of anemia have been reported.[2, 3] The hemolytic episodes occur at an early stage of treatment and are due to the hypersensitivity of the patient to the drug and not, as might be expected, to excessive dosage. With the availability of many new antibiotics, the subsequent side effects associated with sulfonamide administration may tend to be overlooked. It is with this in mind that the following case is reported.

A 6-week-old infant girl was admitted to the Calgary General Hospital on August 7, 1960, with a diagnosis of bilateral bronchopneumonia. S. R. penicillin® 200,000 units twice daily was begun on August 8. At this time the hemoglobin value was 15.6 g. % and white cell count 18,900/c.mm., with neutrophils 20%, stab forms 12% and lymphocytes 67%. Red blood cells showed slight anisocytosis and polychromasia only. On August 9, sulfonamide therapy (sulfaethyldiazole—Solusulpha®) 300 mg./day was added.

The child was apparently slow to respond to treatment, and by August 16 the hemoglobin value was 9.7 g. %, and white cell count 15,200/c.mm., with neutrophils 25%, stab forms 3%, eosinophils 2%, lymphocytes 66% and monocytes 4%. Red blood cells then showed marked polychromasia, numerous microspherocytes and polychromatic macrocytes suggesting rapid red cell regeneration.

The sudden drop in hemoglobin level (6 g. in eight days) and the changes in the blood film suggested a period of acute hemolysis. It was wondered whether the sulfaethyldiazole could have been the provocative agent. The next day the hemoglobin value dropped to 8.6 g. %, and normoblasts were observed in the blood films. Further investigation revealed a normal osmotic fragility curve, a negative direct Coombs test, reticulocytosis of 18% and Heinz bodies in 20% of red cells.

As an experimental procedure to determine whether Heinz bodies could be produced *in vitro*, 100 mg. of sulfaethyldiazole was incubated with 2 ml. of the patient's heparinized blood for one hour at 37° C. Heinz bodies were then demonstrated in 80% of the red cells, whereas none were found in a normal random control blood sample treated in the same manner.

This experiment strongly suggested that the sulfaethyldiazole was the provocative hemolytic agent and that the patient was hypersensitive to this drug. In view of these findings, sulfonamide therapy was discontinued. No further drop in hemoglobin occurred. The child was sent home well on August 22, hemoglobin value being 10.6 g. %.

DISCUSSION

Although hemolytic episodes due to sensitivity to various sulfonamides have been recorded, no

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instances due to sulfaethyldiazole have been noted in the literature. Heinz bodies probably consist of denatured globin derived from hemoglobin. With some drugs, notably acetylphenylhydrazine, the hemoglobin acts as a catalyst in the oxidation of this drug and is broken down in the process. Heinz bodies stain supravitally with most basic dyes and range in size from minute particles to bodies up to 3 microns in diameter.[4] In this case, 1% cresyl blue and 1% methyl violet in saline were tried, but 1% cresyl violet in saline gave the best results. This was also the experience of Beutler.[5]

SUMMARY

Acute hemolytic anemia with Heinz body formation in a six-week-old child during sulfaethyldiazole therapy is reported. *In vitro* incubation of the patient's blood with sulfaethyldiazole produced large numbers of Heinz bodies on staining with cresyl violet. This proved a simple way of confirming the nature of the condition.

REFERENCES

1. HARVEY, A. M. AND JANEWAY, C. A.: *J. A. M. A.*, 109: 12, 1937.
2. WOOD, W. B., JR.: *Ibid.*, 111: 1916, 1938.
3. SPENCE, H. M. AND ROBERTS, G. M.: *New England J. Med.*, 222: 874, 1940.
4. DACIE, J. V.: The hæmolytic anæmias: Congenital and acquired, J. & A. Churchill, Ltd., London, 1954.
5. BEUTLER, E.: *Blood*, 14: 103, 1959.

SHORT COMMUNICATION

SCURVY, AMINOACIDS AND CHROMATOGRAPHY

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THREE CASES of scurvy with associated aminoaciduria have been reported.[1] In these cases the urinary aminoacid picture was studied quantitatively, using an accurate but lengthy separation procedure. This paper is a report of two cases of scurvy in which the abnormal aminoacid pattern was observed by using a simple chromatographic screening method similar to that recently suggested by Ghadimi and Schwachman.[2]

CASE 1.—An 8½-month-old boy was referred to hospital because of a 5-day history of bleeding mouth and painful legs, and a 10-day history of excessive crying and irritability. The infant appeared well developed and nourished, and weighed 22 lb. His skin looked pale but the hemoglobin value was 12 g. %. His diet had consisted of powdered milk and added Pablum and cereals but no vitamins. Clinical and radiological examinations showed the signs of classical scurvy.

CASE 2.—A 9-month-old boy was referred to hospital because of irritability for one month and because he had exhibited diminished spontaneous limb movements for one week. The infant had been fed milk and Pablum, but had not had any vitamins or orange juice for 2 to 3 months before admission. The child looked well developed and nourished, and weighed 16.6 lb. His skin was pale and the hemoglobin value was 12.6 g. %. Physical examination and radiographs showed typical signs of scurvy.

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In both cases the serum ascorbic acid level was under 0.1 mg. % at the time of admission. The urinary ascorbic acid output was under 1 mg. after an ascorbic acid loading test. Chromatograms of the urine showed an aminoaciduria which will be discussed further. Therapy consisted of administration of 100 mg. of ascorbic acid daily and orange juice *ad lib*. In each case the clinical response was, as usual, dramatic: within three days the infants lost their irritability and could be handled comfortably. The gingival bleeding ceased in five days. Radiographic appearances and subperiosteal swellings were still unchanged at the time of clinical recovery.

The pattern of aminoacid chromatograms of urine is not widely used as a diagnostic aid because of the time required to run two-dimensional chromatograms. Recently Ghadimi and Schwachman[2] have suggested the use of circular paper chromatograms as a screening method, reserving the two-dimensional chromatogram for those specimens showing some change from the normal pattern. We have found this to be an excellent approach, as only about 5% of the urine specimens submitted show anything unusual in their aminoacid pattern. Our procedure differs from that of Ghadimi and Schwachman in that we use a butanol-acetic-acid system rather than an acetic-acid-ethanol system as in our experience this gave a sharper resolution of the bands.

METHOD

Apparatus and Reagents

Circular chromatography outfit—14 cm. (Cave & Co., Vancouver, B.C.)

Slotted filter paper—Whatman K.C.T. No. 1—14.5 cm.

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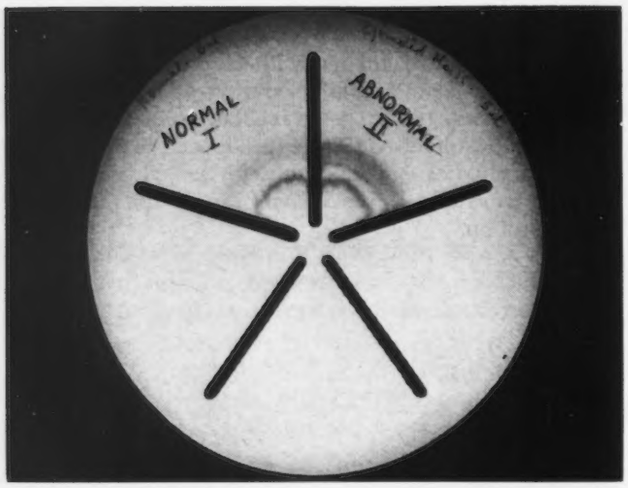

Fig. 1.—Normal and abnormal urinary aminoacid pattern.

Solvent—n-butanol—120 ml.; acetic acid—30 ml.; water—50 ml.

Spray reagent—0.2% ninhydrin in acetone.

Procedure

Ten lambda of urine is applied to the centre of the paper disc at the appropriate slot. Five separate samples can be run. The solvent creeps near to the edge of the paper disc in about one hour. The paper is removed, air-dried and sprayed with ninhydrin.

DISCUSSION

Fig. 1 shows such a chromatogram. We attempt to run a specimen from a normal individual in the same age group as that of the patient whose urine is being studied. Any urines showing either more intense bands or more numerous bands are run by two-dimensional chromatography.

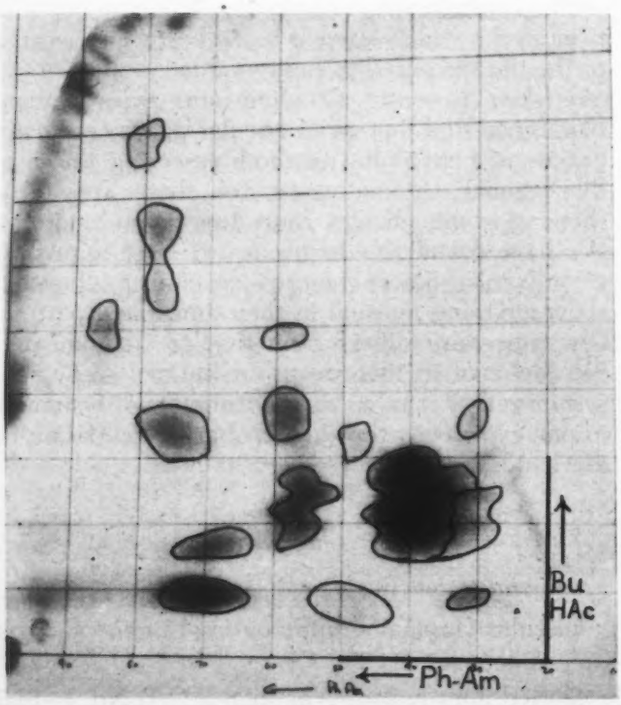

Fig. 2.—Two-dimensional urinary aminoacid pattern from Case 2 before treatment with ascorbic acid.

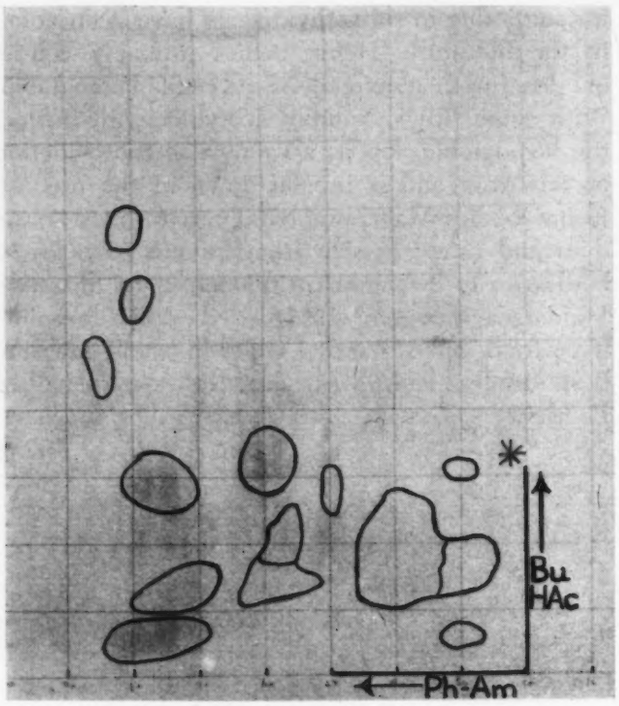

Fig. 3.—Case 2 after clinical recovery from scurvy.

It was in such a survey that both Case 1 and Case 2 were observed. The urine chromatogram of Case 2 is shown in Fig. 1 marked Abnormal II. Fig. 2 shows the same urine run two-dimensionally. Fig. 3 is the pattern after the patient had been clinically cured of scurvy. Figs. 4 and 5 show the patterns of Case 1 before and after treatment. In this case, the pattern in Fig. 5 is essentially normal.

No attempt will be made here to discuss the significance of the appearance of specific amino-acids in the untreated scurvy patient. In general it would appear that phenylalanine and tyrosine, which appear in the upper left quadrant of Fig. 2,

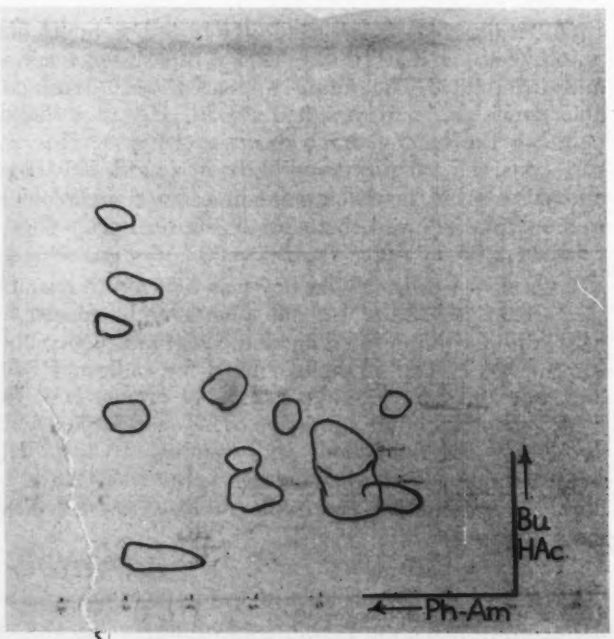

Fig. 4.—Case 1 before treatment.

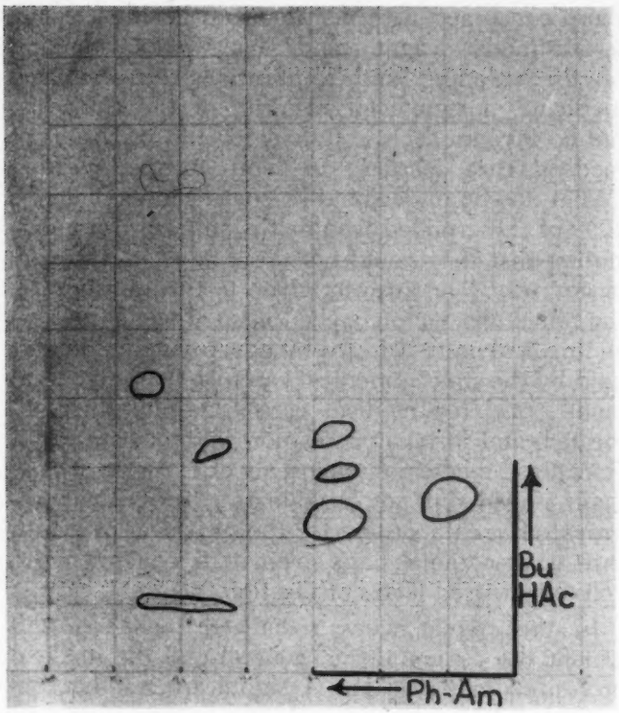

Fig. 5.—Case 1 after treatment.

are characteristic. A normal pattern, as seen in Fig. 5, rarely shows spots in the upper left quadrant. It is well known that ascorbic acid plays an important role in the breakdown of tyrosine into p-hydroxy phenylpyruvic acid, and thus an increase in tyrosine excretion through a simple overflow mechanism would be expected. However, Huisman[3] has shown no increase in plasma tyrosine levels in scurvy. This would imply that a change in renal tubular reabsorption has occurred with regard to tyrosine.

Since this paper was prepared, two other cases of scurvy have been observed. As in Case 2, the aminoaciduria continued for a few weeks after clinical recovery. Also we have found that it is possible to follow the diminution of the aminoaciduria by use of the simple circular chromatogram.

EARLY DIAGNOSIS OF SCURVY

In both cases the bone changes, as seen on the radiographs, must have taken days or weeks to develop. There is no clinical picture characteristic of this early scorbutic stage. Irritability, failure to gain weight, fretfulness and pallor are practically the only manifestations shown by all patients before admission to hospital. Infants exhibiting any of these manifestations between the ages of 8 and 13 months should be suspected of having latent scurvy unless there is reliable evidence of an optimum intake of vitamin C, and should have their urine screened for aminoaciduria with particular attention to excess tyrosine. It is reasonable to assume that the excretion of tyrosine is one of the earliest manifestations of disturbed metabolism due to vitamin C deficiency.

SUMMARY

The aminoaciduria of scurvy can be readily observed by use of a simple circular chromatogram. Details of the technique are given.

We wish to thank Mrs. Joan Dakin for her careful technical assistance and Dr. L. Grisdale for permission to study these two cases.

REFERENCES

1. JONXIS, J. AND HUISMAN, T.: *Pediatrics*, 14: 238, 1954.
2. GHADIMI, H. AND SHWACHMAN, H.: *New England J. Med.*, 261: 998, 1959.
3. HUISMAN, T. H. J.: *Pediatrics*, 14: 245, 1954.

DRUG EVALUATION IN INDUSTRIAL MEDICINE

Techniques are described by Behrend and Jaeger (*Indust. Med.*, 29: 319, 1960) by which physicians may evaluate drugs before adopting them for routine use in occupational medicine. Several of these are illustrated by an example of a study among workers in a clothing industry.

Acceptable technique coupled with careful observation will yield helpful data. All studies in which a comparison is made have some sort of control. The following types are discussed: historical controls, balanced control groups, randomly selected control groups, techniques using the patient as his own control, and comparison of the test drug with a standard drug. Other techniques include the double-blind technique, the use of placebos, and the use of statistics.

Although the control principle does not prevent the patient's personality and environment from influencing his reaction to a drug, it compensates for these shortcomings by ensuring that they extert equal influence in the control and test groups. The double-blind technique does not ensure infallibility, but it does eliminate the influence of the physician's bias and the patient's expectations. In drug studies the use of placebos is often barred for ethical reasons. Statistics do not ensure reliability of the conclusions reached, but can be helpful in assessing the significance of the data.

Reference is made to a recent study in which evaluation was made of a combination of drugs among workers in a clothing industry. The purpose was to test the value of adding a tranquillizing drug to the aspirin-phenacetin-caffeine (APC) combination commonly prescribed for relief of mild and moderate pain. The procedure incorporated the following techniques: the randomly selected control group, comparison with a standard drug, the double-blind technique, and a typical method for recording results. The results indicated no significant difference in analgesic or mood elevating properties of the two tablets. A more extensive study with a larger sample might have revealed different results.

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POLITICAL TRENDS AND THE FUTURE OF CANADIAN MEDICINE

IT is probably no exaggeration to state that from the point of view of Canada's medical profession, 1960 was a highly political year. In the minds of those who indulge in the enlightening, if not always educational pastime of reading newspapers, there can be no doubt that the major political parties have definite plans for the future of Canadian medicine. This fact of life is made even more abundantly clear in the pages of Hansard that record the official reports of debates in the House of Commons for the year just ended. We have been informed by representatives of prominent and powerful labour forces that they too have well-formed designs for the provision of medical care to our fellow citizens.

The voice of that nebulous, but potent and influential entity, the voting public, is speaking with increasing insistence and it is safe to assume that the ears of those who create policy at all levels of government across the length and breadth of our land are carefully attuned to its words. A recently reported survey of public views on the provision of medical services, conducted by the Canadian Institute of Public Opinion (the Gallup Poll),[1] reveals some highly significant and, depending on one's personal viewpoint, startling trends. There is good reason to believe that Canadians are becoming increasingly concerned with security in all its aspects, that they like the idea of government sharing their expenses, and the larger the government's share of these expenses the better will it please them. To many of us who hold the belief that ours is a free-enterprise economy it may come as a sobering surprise to learn that today more Canadians would prefer to work for the government than for a private organization. To an even greater degree than in Great Britain, the people of this country are enthusiastic about present government handling of social services, particularly those concerned with pensions and health. Despite a distinctly vague and hazy understanding of the meaning and implications of socialized medicine, a significant majority of the Canadian public favours such a system for the provision of medical care services. In reply to the question "What do you understand by socialized medicine?", 42% of those polled wouldn't even hazard a guess, stating that they could not describe such a service in any way. The answers given to this question by the remainder were couched in such vague phrases as "medical costs paid for by government", "doctors paid by the state", "medical care run by the government", or "free medical care". Despite their ill-formed, and in many cases non-existent concept of "socialized medicine", almost six of every ten Canadians polled did not hesitate to express their approval of such a system for the provision of health care on a national basis even if its enactment involves increased levels of taxation.

In the public view, socialized medicine will benefit the community in general and the medical profession in particular. A significant number believe that it would ensure better patient care and provide the physician with more time for study and research. A large segment of the public considers the trend towards socialized health measures as an inevitable and desirable goal; in the opinion of a minority only, it would involve a threat to personal freedom and initiative.

The significance of these public attitudes towards health care services should not be ignored or minimized by the medical profession. It is a safe assumption that they are receiving and will continue to receive a sympathetic hearing from those who will influence and determine the policy of all political parties. One of our professional colleagues, whose vantage point as a member of the federal Parliament provides the opportunity for continuous palpation of the sensitive parliamentary pulse, has expressed the view that more surely than ever before, Canadians are travelling the road to universal coverage for medical care services.[2] In this atmosphere of political and public opinion it is a matter of considerable urgency that the responsible and carefully considered, collective opinion and positive recommendations of the medical profession regarding all factors that will affect the future practice of medicine in Canada should be communicated in the clearest, most effective and convincing manner to political parties and to the Canadian public, many of whom are presently ill-informed or uninformed on these matters.

Canada is a democratic nation, and as in any democracy the majority of decisions on social measures are founded on political activity.

Surely, however, there can be no logical argument with the conviction that a heated and emotionally charged election campaign, in which contesting parties are faced with the urge to outdo each other in the attractiveness of their projected

programs, scarcely provides the ideal atmosphere for dispassionate and objective consideration of the future pattern of health care in this country, a matter that will be of such vital importance and profound concern to all Canadians for generations to come. With this conviction, and with the objective of removing the consideration of health and health insurance from the hectic arena of political controversy, the Executive Committee of the Canadian Medical Association on recommendation from the Committee on Economics approached the Government of Canada with a request that there be established a Royal Commission to investigate Canadian health needs and resources, and to study methods of ensuring the highest standard of health care for all citizens of this country.[3] The Prime Minister's immediate announcement in Parliament that a Royal Commission would be constituted for this purpose is now history. The results of this action remain to be seen.

While it is important that the views and positive recommendations of Canada's doctors should be clearly and effectively presented to politicians and to the public, it is likewise necessary and desirable that the medical profession be kept informed, insofar as possible, of current developments and activities within the political sphere that bear upon matters affecting the practice of medicine in Canada. In an endeavour to contribute such information to the profession, a new section of the *Canadian Medical Association Journal* has been established under the heading of *Medical News from Parliament*. Dr. Hugh M. Horner, Member of Parliament for Jasper-Edson, has graciously consented to act as the Journal's parliamentary correspondent and will attempt to provide our readers with a commentary on the trends in parliamentary discussions that are of interest and significance to the medical profession. This section will take the general form of a periodic newsletter whose frequency of publication will be determined in the light of subsequent experience. It will, of course, appear in the Journal only during that period of the year in which Parliament is in session. Dr. Horner has for some time held the conviction that doctors should be more adequately informed concerning the implications of political activity to medical practice, and we feel safe in assuring him that readers of the Journal will look forward to his contributions in the days to come.

REFERENCES

1. SANDERS, B. H.: *Ontario M. Rev.*, 27: 1159, 1960.
2. HORNER, H. M.: *Canad. M. A. J.*, 83: 123, 1960.
3. News and views on the economics of medicine, *Ibid.*, 83: 1393, 1960.

RECENT DEVELOPMENTS IN TREATMENT OF SOME BLOOD DYSCRASIAS

MASSIVE doses of corticosteroids have been used in the treatment of acute leukemias with variable results. Bouroncle, Doan and Wiseman[1] administered prednisolone to 30 patients with acute leukemia for 9 to 14 days with an average total dose per course of 9300 mg. and obtained complete remissions in only seven patients, of whom five had acute lymphatic leukemia and two acute monoblastic leukemia. However, all patients felt immediately better, their appetite increased and their temperature fell to normal levels within one to two days. Bernard[2] of Paris reported his experience with large doses of corticosteroids at the 15th Annual Conference of the Swiss Hematological Society, held on June 10, 1960, in Zermatt. He treated acute leukemias with prednisone in doses of 2 to 4 mg./kg. daily during the acute phase and administered 6-mercaptopurine during the entire period of remission. In more advanced and resistant cases even higher doses of steroids were given (5 mg. of prednisone per kg.), followed by the administration of amethopterin. With this method remissions were observed in 91% of cases, with an average duration of seven months for initial remissions.

Bernard also described recent experimental work which may eventually lead to more effective treatment of leukemias. The identification of cytostatic agents that act selectively on leukemic cells will require more adequate knowledge than is presently available concerning the biochemical differences between normal and leukemic cells. Currently, attempts are being made to overcome this difficulty by combining cytostatic drugs with vector substances which have an elective affinity for leukemic cells. Antileukemic immunoglobulin to which amethopterin has been chemically attached has produced encouraging results in mice and may prove useful in humans. Antinucleic acid immunoglobulin has been employed in the treatment of human leukemia with discouraging results but its failure to date may have been due to the unsatisfactory conditions under which the trial was carried out. Bernard also reported personal experience with transfusions and homologous bone-marrow grafts. Pretreatment of the patient by total body irradiation with lethal doses (700 to 1000 rad) is a prerequisite for homologous bone marrow transfusion. When immunity reactions are reduced by the underlying blood-disease, as in some patients with Hodgkin's disease, it may be possible to achieve successful bone marrow transfusion following sublethal doses of irradiation.

Dubois-Ferrière and Kalaçi[3] treated 40 patients with acute lymphomas and acute lymphoblastic leukemia, with prednisone in doses as high as 1 g. daily, followed by the administration of nitrogen mustard or cyclophosphamide. In most of these

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cases, repeated courses of such treatment were tolerated. This combined treatment achieved remissions in over 90% of cases, the length of the first remission ranging from 9 to 18 months. There were remarkably few side effects although the danger of fungus infection and of other infections is great if the treatment is prolonged. Dubois-Ferrière believes that it is wiser to withhold the use of antibiotics until infection develops than to use these drugs on a prophylactic basis with a view to the prevention of complicating infections. Although this form of treatment is not as a rule indicated for chronic lymphatic leukemia, it has occasionally been of value in causing regression of particularly resistant adenopathy and splenomegaly in this disease. In patients with lymphomas or lymphogranulomas, this treatment may permit the successful use of antimetabolites which had previously been of no benefit to these patients.

Di Guglielmo of Florence[4] has been using corticosteroids in fairly high doses, in combination with ethyl-urethane, estrogens and cyclophosphamide for patients with myeloma or Waldenström's macroglobulinemia. In the latter disease the reactions indicating the presence of abnormal serum proteins became normalized after therapy, sedimentation rates decreased precipitously, and the serum-hexoses dropped from 300 mg. % to 150 mg. %. The electrophoretic pattern, grossly abnormal before treatment, became practically normal following the administration of 1750 mg. of prednisone.

In the discussion that followed these reports the danger of infection in the course of steroid treatment was stressed and many speakers agreed regarding the advantage of combining high-dosage steroids with cytostatics and other known antimetabolites.

These results are of considerable interest and it appears that such therapeutic measures may be of some benefit to selected individual patients with acute leukemia as well as to a small number with chronic leukemia. Prednisone in doses of 1 g. daily, or the equivalent dose of other corticosteroid analogues, does not appear to have any serious undesirable effects although they are expensive. In discussing the potential significance of these observations, Di Guglielmo expressed the opinion that in these diseases, as in the case of all neoplastic disorders, a rational approach to treatment should be directed towards the prevention of proliferation of malignant cells rather than attempt to destroy such cells after they have begun to proliferate.

W.G.

REFERENCES

1. BOURONCLE, B. A., DOAN, C. A. AND WISEMAN, B. K.: *Acta haemat.*, 22: 201, 1959.
2. BERNARD, J.: *Schweiz. med. Wchnschr.*, 90: 1177, 1960.
3. DUBOIS-FERRIÈRE, H. AND KALAÇI, S.: *Ibid.*, 90: 1182, 1960.
4. DI GUGLIELMO, R.: *Ibid.*, 90: 1189, 1960.

HAIL AND FAREWELL

THE LONDON Letter that appears in this issue marks the end of an association that has been a source of entertaining and shrewdly phrased information to *C.M.A. Journal* readers for the past fifteen years. Accompanying this edition of the *Letter* to the editorial office of the Canadian Medical Association came the following saddening message which, although it was addressed to the Editor, concerns all of this Journal's readers:

In enclosing the December London Letter, I am afraid that I have to add that it is also my last one. In view of my increasing commitments I have to curtail some of my activities, and I have reluctantly come to the decision that the London Letter is one of the things I must give up. Needless to say, this has not been an easy decision to make, because I have particularly enjoyed this assignment ever since I took it over some fifteen years ago. . . . Finally, may I say how much I have enjoyed my long association with the Journal. I sever this association with the greatest of reluctance . . .

Yours sincerely,
William A. R. Thomson.

Dr. Thomson, who has recently been described by his distinguished journalistic colleague, the editor of the *New England Journal of Medicine*, as "the versatile and canny Scottish editor of the *Practitioner*", has consistently demonstrated his uncanny ability to assemble and interpret the news of the British medical scene and to express it in a style that is both scholarly and informative, diffusely infiltrated by wit and wisdom. In addition to his outstanding contribution to medical journalism as co-editor of the *Practitioner*, he is the author of Black's Medical Dictionary and of a learned volume entitled "The Searching Mind in Medicine", his most recently published literary product.

On behalf of *C.M.A. Journal* readers we express to him sincere appreciation of a job well done, a deep sense of regret that he must terminate his assignment as our London Correspondent, and our best wishes for the success of his future endeavours.

To offset the loss of the services of this faithful contributor, however, comes the welcome news that the authorship of the London Letter will remain in the capable hands of an experienced journalist and friend, Dr. Stanley S. B. Gilder, who is of course familiar to all as the former occupant of this editorial office and as the current editor of the *World Medical Journal*. Dr. Gilder may be assured that his Canadian readers look forward with anticipation to a long and mutually gratifying association with our new London Correspondent.

LETTERS TO THE EDITOR

CANADIANS SHOULD PUBLISH IN CANADIAN JOURNALS: THE OTHER SIDE OF THE STORY

To the Editor:

In the November 26 issue of the Journal (83: 1164, 1960) Dr. E. H. Bensley has published an article in the *Men and Books* column in which he urges that Canadians have an obligation to publish their papers in Canadian journals. It seems to me that the other side of the picture should also be stated. In other words, Canadian journals have some responsibility to publish the writings of Canadian research workers in both the laboratory and clinical field. Also they should do this when the results or theories are not plainly impossible even though members of the profession in some of the large cities do not believe or agree with the ideas expressed. This is not being done at present, as my personal experience will illustrate.

During the years 1949 to 1959 I had 24 articles published. Five were in the *Nova Scotia Medical Bulletin* and only one in the *C.M.A. Journal*. Eighteen of the 24 papers (including four of those published in the *Nova Scotia Medical Bulletin*) had to do with work which I have been doing for over 30 years in the field of immunization, using doses of bacterial antigen-antibody which are five to ten times as large as those which are used by other workers or which have been published in other reports. It seems fair to suggest that neither the editors nor the members of the editorial board know anything about this subject. If they do they have been very unfair to the rest of the medical profession in Canada and elsewhere in not having published the results, because the results of such treatment in a great variety of conditions are very good and very much better than those which are ordinarily reported as being obtained by other methods of treatment. May I give a few examples of what I mean?

A few years ago, when an English doctor made some clinical tests and found that a considerable percentage of several hundred patients seemed to be protected against the occurrence, severity and complications of the common cold by use of a bacterial vaccine, not only was his work published in a British journal but it was commented on quite favourably in the *C.M.A. Journal* as a matter which should be further investigated. In 1951, however, when I submitted a paper on the common cold reporting equally good or better results from the use of the high-dosage treatment with mixed respiratory antigen-antibody, the paper was rejected by the editor as being "insufficiently well supported". A short time later it was published in a medical journal in the United States. In the same year (1951) I offered the editor of the *C.M.A. Journal* a paper on psoriasis. The previous year the *British Journal of Dermatology and Syphilology* had published a preliminary report in which I presented some 20 consecutive unselected cases of psoriasis which seemed to respond rather miraculously to high-dosage treatment with bacterial antigen-antibody. I suggested that the treatment should be further investigated in a large number of cases. The paper offered to the *C.M.A. Journal* was a report on another series of cases. The editor said "I do not feel, however, that it is very convincing." However, the same material has been presented in other papers, and a considerable number of dermatologists in the United States are reporting to me privately that they find the treatment very successful. The action of the *C.M.A. Journal* has meant that the Canadian physicians have been denied the opportunity to test and find out for themselves what can be done with this method of treating psoriasis. Of course a few have learned about it by word of mouth, and have told me personally that they have used it successfully. In one case an elderly physician who had psoriasis himself cleared up his condition completely, and successfully treated two friends who had also had it for years. As a matter of fact, the attitude of the editorial board of the *C.M.A. Journal* has been that they are censors who should see to it that the tender mind of the average Canadian physician is not be exposed to anything which they (the editors) do not consider to be proper and fitting. This attitude was expressed on one occasion some years ago by the editor himself.

Since 1951, on more than one occasion, I have offered a paper to the *C.M.A. Journal* on some aspect of immunization with high doses of bacterial antigen-antibody, not expecting it would be published but more or less to have it on record that it was *first offered* to the *C.M.A. Journal*. Later the article was offered to another journal outside Canada (frequently a specialist one) and it was accepted and published. July 1960 represents the latest date of a refusal by the *C.M.A. Journal* to publish something along this line. In that article I reported eight cases of pyoderma in which the patient carried the same phage-pattern staphylococcus in the nasopharynx as was obtained from the skin lesions. Six to eight inoculations of bacterial antigen-antibody cleared the skin condition—as had occurred *quite routinely* in scores of cases for many years! At this point in each of the eight cases the carrier state was still present; but with another six or eight inoculations, and reaching twice the dosage, in every case the carrier state had disappeared. This was suggested as a possibly rewarding line of approach to the staphylococcal problem. The editors did not seem to think so.

From the experiences described I think it is fair to draw the following objective conclusions:

1. The work I have been doing over a considerable number of years is of interest to specialists in the fields of allergy, immunology, dermatology, and otolaryngology, as well as to the general practitioner.

2. My articles are written in a manner which is quite satisfactory to the editors of a considerable variety of medical journals—being usually published without any editorial suggestions or changes. In one case I was requested to contribute an article on this subject to a specialist journal.

3. At least some of our Canadian doctors would like to learn more about the new and original work which I have been doing in this field. For example, when I presented a Scientific Exhibit at the C.M.A. convention a few years ago, a considerable number asked me why I had not published this work. I was forced to point out to them that it had been published in American

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and British journals, and that I had reprints available from those articles, but that their own journal had consistently refused to publish anything on this subject.

I have good reason to believe that my experience is not entirely isolated, but that certain other Canadians who have done new and original work which is not known or not approved of by certain people in Toronto and Montreal have found it difficult or impossible to get this work published in Canada.

In conclusion, may I repeat my original contention that Dr. Bensley was describing only a half truth when he said that Canadians should publish in Canadian journals. The other part is that Canadian journals should publish more of the work of Canadians.

562 Dunn Avenue, K. A. BAIRD, M.D.
Lancaster, N.B.

INTRA-ARTICULAR CORTICOSTEROID THERAPY AND CHARCOT-LIKE JOINT CHANGES

To the Editor:

Dr. Riggall (*Canad. M. A. J.*, 83: 1271, 1960) should take to task his informant at the National Orthopaedic Hospital who stated that "injection of steroids into joints had been abandoned . . . because of atrophy of joint structures."

Having myself injected a modest total of some 8000 joints with steroids, I have kept a weather eye open for dangers in a therapy which has often seemed too good to be true.

In the *British Medical Journal* (1: 1392, 1960) Sweetnam and Mason of The London Hospital, and Murray of the Royal National Orthopaedic Hospital showed that in the hip joint, progressive deterioration occasionally occurred under long-term systemic or intra-articular (into the hip joint) steroid therapy. This was attributed to the concatenation of three main factors: (1) the high mechanical stresses in the femoral head and neck in weight-bearing; (2) osteoporosis due to local or systemic steroids; and (3) reduction of guarding by protective reflex muscle spasm, due to the reduction in pain under steroid therapy.

These factors led to multiple trabecular stress fractures, leading to a radiographic appearance resembling Charcot's joint.

Now, surely, this paper is not going to lead us to "abandon intra-articular steroids". It is going to lead us to take special care in long-term steroid medication systemically, and perhaps to shun prolonged intra-articular steroid therapy for hip disease.

No doubt, it will also be worth while to look out for Charcot-type changes in other lower limb joints when under steroid therapy. To anticipate future statistics on the basis of present clinical impressions, however, I think that most patients, if apprised of the dangers in terms of betting odds, would usually *ask* for intra-articular steroid injection.

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THE LONDON LETTER

(From our own correspondent)

THE HEALTH OF EXECUTIVES

For the second year running, the Chest and Heart Association (still better remembered by many under its old name of the National Association for the Prevention of Tuberculosis) has held in London's famous Festival Hall a one-day conference on "The health of executives". The highlight of this year's conference was the doyen of American cardiology, Dr. Paul White, who, in his quiet unostentatious manner, held his audience's attention while he expounded his thesis of moderation in all things. Inevitably for a conference such as this, with an entirely lay audience, the organizers must recruit some of the more ebullient of the profession as lecturers, but it was interesting to note the attention given to the quietly delivered lecture on "Helping the healthy executive" by Dr. L. G. Norman, chief medical officer to London Transport. After pointing out that executives probably formed one of the healthiest groups of men in industry, he added this warning: "Unless health education is properly conducted, we may create a reign of terror for executives: a haunting fear that coronary thrombosis, high blood pressure, or some other disorder, is lurking just around the corner."

BIOLOGICAL ENGINEERING SOCIETY

Although it is only one aspect of the problem, it is the rapid advance in medical electronics that has brought to the fore the need for increasing co-operation between the biologist and the engineer if the present rate of progress in medical research is to be maintained. It was with a view to obtaining such co-operation that earlier this year steps were taken to found the Biological Engineering Society, under the enthusiastic presidency of Professor Ronald Woolmer, professor of anesthesia at the Royal College of Surgeons of England. At the first scientific meeting of the Society, held recently at the National Institute for Medical Research, Sir Charles Harrington, the director of the Institute, suggested that in the years to come biological engineering would be as acceptable a discipline as is biochemistry today. The range of demonstrations at this meeting gave ample evidence of the scope for this new paramedical science. They ranged from metallic implants in orthopedic surgery and artificial voice appliances to kinetic gas analysis.

FOOD PROCESSING

Much interest has been aroused by the announcement of the setting up of a new research organization, the British Industrial Biological Research Association, to study the effect of food processing on health. Supported by leading companies in the food, chemical, essences, plastics, packaging and cosmetic industries, the aim is to establish a research station to investigate the effect of the many substances used in food manufacture, either as processing aids or for flavouring and colouring food. Equally important will be the investigation of the substances which may get into food from pesticides, plants used in food manufacturing, or packaging material. Although some of the larger com-

panies have their own research facilities, hitherto there has been no co-ordinated national organization to tackle the problem. The new Association is to receive a grant from the Department of Scientific and Industrial Research, and this, together with the financial help already promised by 90 companies, should provide adequate support for the new research institute which it is proposed to build and which is expected to be in action by 1962.

THE INCIDENCE OF RHEUMATISM

Over 14% of the total population of Britain—5¾ million to be precise—are suffering from some severe form of rheumatism, according to a statement just issued by the Empire Rheumatism Council. This figure is an estimate based upon the preliminary findings of two surveys carried out by the Council's Field Survey Unit: one covering 1700 individuals in industrial Lancashire; and one covering 900 individuals in rural Wensleydale. In view of the size of this sample, it is considered adequate to give a reliable indication of the prevalence throughout the country. So far as rheumatoid arthritis is concerned, the average incidence was found to be 2.5% for men and 6.1% for women. This means that at any one time there are around 470,000 men and 1,270,000 women, a total of 1,740,000 afflicted by the disease in Britain. The incidence, of course, increases with age, and the figures from this survey indicate that three out of every 20 women over the age of 54 are handicapped by the disease.

Even more startling are the figures for osteoarthritis. Changes caused by osteoarthritis begin to appear in about one in ten individuals at the age of 24, and by the age of 65 some 97% of men and 98% of women have radiological evidence of this disease. Fortunately, in about a third of these individuals there is no incapacity but, even so, this means that 3¾ million people over the age of 65 have moderate or severe osteoarthritis. To round off the picture it is only necessary to add that spondylitis and gout each had a prevalence of 0.3%, which is equivalent to a total of 120,000 cases of each throughout the country.

London, December 1960 WILLIAM A. R. THOMSON

MEDICAL NEWS IN BRIEF

PROGRESS IN KNOWLEDGE CONCERNING DIABETIC ACIDOSIS AND ITS TREATMENT

In recent years new knowledge of the relationships between carbohydrate and fat metabolism and of their dependence on endocrine factors has been forthcoming. Foremost in this progress is the awareness of the importance of the pentose-phosphate pathway over which up to 50% of all nutriments absorbed as glucose are oxidized. Previously, diminished glycolysis alone was believed to be responsible for the increased production of ketones. Insulin stimulates synthesis of fatty acids from carbohydrates and the take-up of fatty acids from the blood by the tissues. Its antagonists, adrenaline, growth hormone and glucagon, cause release of fatty acids to the blood. It is believed that lipolysis is stimulated by these substances and that this causes secondary liberation of fatty acids from the glycerides of tissue fat. In the absence of insulin, these antagonists free large amounts of fatty acids into the circulation to arrive in a liver already seriously compromised in its ability to effect fat synthesis. The pentose-phosphate pathway, which depends on the presence of insulin, cannot contribute to complete oxidation of the fatty acids which condense into aceto-acetic acid. Although peripheral tissue is able to take care of some of the ketones, the marked increase of ketone bodies is too great for adequate disposal by this means and they overflow from the liver throughout the body tissues.

The body's defence mechanisms against ketosis are as follows: The kidney prevents loss of cations by acidification of urine and excretion of unassociated free acids. In addition, the kidney is able to synthesize ammonia with the help of glutaminase and thus save cations. This defence mechanism comes into play after acidosis has been in progress for one to two days, reaching its maximum on the second or third day, and lasts for several days after the acidosis has been overcome, permitting the organism to recapture some of its lost cations. The blood and the lungs have separate defence mechanisms. Large amounts of glucose in the urine produce osmotic diuresis, but as long as patients drink and replace their lost electrolytes by eating, decompensation is prevented. Vomiting and massive hyperventilation produce negative fluid balance, increased viscosity of the blood and diminished blood volume. Circulatory collapse, shock and irreversible hypoxemic damage to the organs follow.

Diabetic acidosis has a marked influence on the activity of insulin. Three factors are considered to decrease insulin activity: (a) acidosis, (b) overactivity of the adrenal cortex, and (c) appearance of insulin antagonists.

While it is well established that diabetic acidosis *per se* lowers insulin sensitivity, there is no current knowledge of experimental evidence of insulin sensitivity in patients with non-diabetic acidosis. Increase of corticosteroids as a consequence of the stress of diabetic acidosis would not explain the ten-fold or greater reduction of insulin sensitivity of the body in pre-coma or coma. Insulin antagonists have been demonstrated in diabetic acidosis and it is known that one antagonist is associated with the alpha-1 globulin fraction, that it is not dialysable, and that it is destroyed by heat and by chymotrypsin. It is quite distinct from insulin antibodies found in diabetic and non-diabetic persons who have received insulin. It is not identical with the beta-lipoprotein which neutralizes insulin and which is partially under the influence of growth hormone and corticosteroids. It is probable that this alpha-1 globulin antagonist is chiefly responsible for the tremendously increased insulin requirements in diabetic acidosis.

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Intravenous drip treatment with insulin is advocated because it is less wasteful of insulin and can be adjusted according to requirements. Studies in their laboratory convinced Rossier and his colleagues (*Schweiz. med. Wchnschr.*, 90: 952, 1960) that the mild alkaline solutions used for intravenous infusion have no deleterious effect on insulin and this was an additional reason why the intravenous drip method of treatment of diabetic acidosis was adopted. In 16 patients who were so treated, normalization of blood sugar and relief of acidosis was achieved in an average of 8½ hours. On an average, 2.8 litres of fluid and 320 units of regular insulin were necessary to achieve these results. In no case was a secondary rise of blood sugar observed after insulin therapy was started. Intravenously administered insulin disappears after continuation of the infusion within one hour at the latest so that no late effects of the insulin are to be feared.

A brief summary of the technique used for investigating and managing diabetic acidosis is presented. The intravenous solution consists of regular insulin in one-third physiologic saline, one-third sodium bicarbonate solution (14 g./l.), and one-third distilled water. If no renal or circulatory damage is present, the following dosage schedule is employed: First hour—1 litre containing 100 units of regular insulin; 2nd to 4th hour—1 litre containing 100 units of regular insulin; 5th to 12th hour—1 litre containing 50 to 200 units of regular insulin; 13th to 24th hour—1 litre with insulin as required, changing to regular insulin subcutaneously as soon as the patient's condition permits. In the presence of renal or circulatory damage, hydration must be accomplished more carefully. In shock noradrenaline is added to the infusion.

THE LATEX FIXATION TEST AND LEPROSY

Numerous studies have emphasized that the latex fixation test is positive in many diseases other than rheumatoid arthritis. Few reports have attempted to define possible clinical implications of this reaction in nonrheumatic diseases. In order to learn more of the biological significance of this reaction, 101 patients with leprosy in the U.S.P.H.S. Hospital, Carville, were examined by Cathcart and co-workers with especial regard to manifestations of leprosy and arthritis (*Arthritis and Rheumat.*, 3: 436, 1960). X-rays of hands and feet, and present and past laboratory findings were reviewed and serologic studies carried out.

Twenty-four of these patients had positive latex fixation tests using inactivated serum. In an additional 20 patients the test was positive using a euglobulin fraction. Fifteen patients had positive sheep cell tests on the serum. Independent clinical evaluation indicated that only three patients had probable rheumatoid arthritis. There were no differences in the clinical manifestations, duration or course of leprosy between the groups with positive and negative reactions. The incidence of amyloidosis was 30% in the latex positive group. There was also a higher incidence of syphilis, diabetes and tuberculosis in the positive group. Prior absorption by lepromin or tuberculin removed the factor responsible for a positive latex fixation test in all but 3 of 20 sera from leprosy patients used as controls. Serologic reactions with denatured gamma globulin and antigen-antibody complexes, as well as ultracentrifuge studies, indicate that agglutinating factors in leprosy and rheumatoid arthritis are similar if not identical.

(Continued on advertising page 32)

Medical News from Parliament

On November 17, Parliament opened, and the Government presented its Speech from the Throne. The actions predicted by the speech cover a wide range of activities. Many are aimed at stepping up economic activity and overcoming Canada's chronic problem of unemployment.

However, there is news in the Throne Speech which has direct relation to the medical profession. Reference is made to steps that the Government will take in encouraging Canadian youth to participate in amateur athletics. Part of the impetus for such government action certainly stemmed from the address by our Past President, H.R.H. The Prince Philip, Duke of Edinburgh, at his inaugural in 1959. Physical fitness in a nation which becomes more and more mechanized is being recognized by government as a problem. I am sure that the medical profession will welcome such action to give to young Canadians the opportunity to participate in amateur athletics. The real problem will, however, still be to convince individuals that such athletics will be of benefit to them.

Also in the Throne Speech, the Government gave notice that it will ask Parliament to extend Federal hospital construction grants for five years beyond March 1963. This will allow our hospitals and provincial and municipal officials to plan ahead. Nowadays, the planning and blueprinting of new facilities and extensions to present hospitals takes almost as long as the actual construction, so that there was a real need to have definite advice as to what the Government intended to do in this regard.

It will be recalled that in 1958, Federal Government assistance under the Hospital Construction Grants was increased to $2000 per hospital bed, regardless of type. This was double the previous grant for active treatment beds. In addition, funds were made available to meet one-third of the cost of approved alterations and renovations to existing facilities. The Provinces must at least match the Federal contributions under the grant.

In the first ten years under the hospital grants program, aid was given to the construction of 68,743 beds, 9112 bassinets, 12,730 nurses' beds and other bed equivalents to 7800.

With the Hospital Insurance and Diagnostic Services Act now in process of being extended to all provinces of Canada, hospital construction and renovation will be required to meet the demands for them. This extension will provide for these grants to 1968 at least.

HUGH M. HORNER, M.D., M.P.

MEDICAL MEETINGS

SOUTHWESTERN ONTARIO REGIONAL MEETING, THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

In an endeavour to expand its activities in the field of graduate medical education, the Royal College of Physicians and Surgeons of Canada approved in 1958 a plan for holding regional meetings. The first such meeting took place in Halifax, N.S., in October 1959, while the second highly successful regional meeting was held under the sponsorship of the University of Western Ontario and its affiliated hospitals on November 15 and 16, 1960. Individual invitations were sent to all 601 certified specialists in the southwestern Ontario area and open invitations were extended to all qualified members of the medical profession in that region. Well over 300 registered for the two-day meetings which were planned in four sections, medicine, obstetrics and gynecology, pediatrics and surgery. This stimulating program was the culmination of a great deal of effort on the part of the nucleus committee consisting of Dr. A. D. McLachlin, Chairman, and Drs. J. B. Collip, F. S. Brien, R. A. H. Kinch and J. C. Rathbun.

Excellent luncheons were served on both days at the Victoria Hospital and the Medical School. The regional dinner was held on November 15 at the London Hunt and Country Club with Dr. Donald A. Thompson, President of the College, as the speaker. An interesting program for the ladies was prepared by a committee convened by Mrs. R. A. H. Kinch.

It was a pleasure for this reporter to attend many of the meetings. The comments that follow pertain to features of these meetings that may be of general interest. Unfortunately one person cannot attend all sessions. There were four guest speakers. Dr. G. R. Brow of Montreal spoke on the subject of extracardiac conditions that produce changes mimicking those of myocardial infarction. Dr. Brow was also a very effective panel member in the discussion on cardiac arrhythmias, for which Professor Brien was the moderator. Dr. Warren S. Wheeler, professor of pediatrics at Ohio State University, discussed problems of infections in the newborn, and acted as panel member in the discussion of other neonatal problems, with Dr. G. H. Valentine as chairman. Dr. K. T. MacFarlane of Montreal spoke on the topic of enterocele and vaginal vault prolapse and acted as a discussant in clinical presentations. Dr. W. C. MacKenzie of Edmonton gave two outstanding presentations concerning diverticulitis as a surgical disease and the choice of operation for duodenal ulcer. In addition he took part in a panel discussion on acute injuries of the thorax and abdomen, with Dr. A. J. Grace as the moderator.

Dr. A. G. Ramsay, in discussing acute renal tubular necrosis, provided a case presentation of a patient who recovered from this disorder following rupture of an abdominal aortic aneurysm. He reviewed the medical management of renal tubular necrosis, including the role of hemodialysis. Dr. L. Reese, in reviewing experience with the artificial kidney, made a plea for its more widespread use as a safe and in many instances a life-saving measure. Indications for dialysis in eight patients were presented, five of whom had acute renal failure, two suffered from the effects of dializable poisons and one had chronic renal failure. Indications, techniques and results of percutaneous and open renal biopsy were discussed by Dr. L. N. McAninch. No serious complications in children and adults have so far been encountered with this procedure in his experience. Dr. M. C. Harvey of Kitchener reported on five patients with retroperitoneal reticulum cell sarcomas encountered during a relatively short period of less than two years.

The cardiovascular system received ample and also very practical attention. In addition to the excellent presentations by Dr. Brow and the panel moderated by Professor Brien, Dr. G. W. Manning gave a critical appraisal of nonspecific electrocardiographic changes and impending myocardial infarction. The difficult problem of prognosis was dealt with by Dr. L. D. Wilcox, while Dr. J. A. Lewis reviewed work on new drugs in the treatment of hypertension.

Nitrogen mustard has been administered to patients at the time of operation for cancer to determine its safety and also to assess whether this drug will lower the incidence of recurrence. Reporting on 59 patients treated with this agent, Dr. J. A. McCredie suggested that it can be safely introduced into the lumen of the gastrointestinal tract and into the peritoneal cavity. It should not be used in operative wounds but can be administered by the intravenous route with safety. Results of experiments performed in rats have confirmed these clinical observations. Dr. J. K. Wyatt spoke on adjuvant chemotherapy in genitourinary surgery with particular emphasis on the polyfunctional alkylating agents and antimetabolites, and the satisfactory results following their use for four patients. He expressed the opinion that this field merits further investigation. Dr. E. K. Lyon of Leamington reported on a study of the use of antibiotics and the incidence of infections in a small hospital. This clearly indicated that prophylactic use of these drugs should be discontinued and that they should be employed only when specifically indicated by the results of careful bacteriological and resistance studies.

A follow-up review of 30 tibial plateau fractures treated between 1953 and 1958 was presented by Drs. J. Watt and J. C. Kennedy. On the basis of these observations they presented a plan of treatment for the various types of fractures encountered. Peritalar dislocation should be suspected when there is severe varus or valgus deformity of the foot following injury. This was emphasized by Drs. J. R. Barber and R. A. Haliburton of Windsor. Closed reduction was employed in six patients with this type of injury and on follow-up all had some limitation of inversion-eversion of the foot. Avascular necrosis of the talus did not occur. Dr. H. S. Cameron discussed the very practical problem of "missed" fractures. He emphasized that many fractures can be very easily overlooked unless one retains at all times an extremely high index of suspicion regarding the possible presence of such bone injuries.

Management and prognosis of fractures are to a varying degree governed by the associated damage to soft tissues. This problem was reviewed by Dr. Sober, who also emphasized that soft tissue injury can indeed be

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the determining factor at times. Dr. D. G. Marshall discussed esophageal atresia, which is the most common alimentary tract anomaly encountered at the Victoria Hospital, London. He presented data on a series of six patients with this disorder. The problem of sclerosing cholangitis of the common bile duct developing in the early postoperative period following cholecystectomy and producing an obstructive type of jaundice was reviewed by Dr. W. Rolland of Brantford. Two recent cases illustrating this complication and factors of possible significance in its etiology were discussed. Dr. A. J. Grace reviewed experience with penetrating duodenal ulcers. This confirmed their notorious resistance to medical management and their liability to complications. A review of 33 patients subjected to primary splenectomy between 1951 and 1960 was presented by Dr. C. D. Keeley of Chatham.

Sphincter spasm is commonly seen in association with anal lesions. If prolonged, fibrosis with permanent contractions may occur. The significance of this lesion was emphasized by Dr. T. D. McLarty and its management was discussed. Dr. D. W. B. Johnston reviewed the management and follow-up of 83 patients with ulcerative colitis. Of these, 42% were treated surgically and 58% received medical management. The mechanism and symptomatology of postoperative respiratory failure was discussed by Dr. W. E. Spoerel. He particularly emphasized the indications for use of controlled respiration and management while in the respirator.

A case presentation of a patient with fatal trophoblastic disease was discussed at a clinico-pathological conference by Drs. R. A. Kinch, M. S. Smout and D. P. Swartz. Emphasis was placed on the value of sensitive serum assays of chorionic gonadotrophin in the follow-up and therapy of this condition. Dr. R. N. Tindale of Hamilton discussed abdominal pregnancy and presented a detailed review of 11 patients with this condition. Dr. L. N. McAninch stressed the importance of an accurate diagnosis when urological complications are suspected. An analysis of 100 consecutive cases of carcinoma of the endometrium treated at the London Clinic of the Ontario Cancer Foundation was presented by Dr. H. H. Allen. Dr. R. A. H. Kinch discussed in detail the management of prolonged retention of a dead fetus. Knowing that fibrinogen therapy can be dangerous and that hypofibrinogenemia, after retention of the dead fetus for five weeks or more, occurs in about 10% of cases, a "hands-off" policy was considered inadvisable. In such cases the induction of labour by the administration of relaxin and Syntocinon was practised. Dr. E. R. Plunkett presented evidence suggesting that relaxin, an ovarian hormone produced largely during pregnancy, plays a previously unsuspected role in thyroid function, possibly mediated through the thyroid-stimulating hormone of the pituitary.

A. H. NEUFELD

GENERAL PRACTICE

FIFTH ANNUAL SCIENTIFIC ASSEMBLY, COLLEGE OF GENERAL PRACTICE OF CANADA, VANCOUVER, MARCH 27-30, 1961

THE FIFTH Annual Scientific Assembly of the College of General Practice of Canada, to be held in Vancouver from March 27 to 30, 1961, will provide a valuable opportunity for the Canadian G.P. to keep pace with medical progress in 1961. Twenty-four medical authorities will take part in the four-day program, which will include three symposia. For College members, attendance at the sessions will provide study credits. The program is as follows:

Monday, March 27

Morning Session: Canadian Tuberculosis Association Lectureship: Viruses in Respiratory Disease—Prof. Thomas Anderson, Glasgow; Psychosomatic Respiratory Manifestations – Dr. T. A. M. Peet, Victoria, B.C.; Bronchite aïgue – Dr. J. M. Huot, St. Boniface, Man.; Acute Bacterial Pneumonia—Dr. W. M. Kirby, University of Washington.

12.30 p.m.: Luncheon. Address: Dr. J. G. Walsh, President, American Academy of General Practice.

Afternoon Session: Symposium on "Flu"—Prof. Thomas Anderson, Dr. J. M. Adams, Dr. W. M. Kirby and Dr. J. A. Flanagan; Laryngo-tracheobronchitis—Dr. J. M. Adams, Los Angeles; Middle Ear Infections—Dr. H. P. House, Los Angeles.

Evening: B.C. Division and Chapter Meetings.

Tuesday, March 28

Morning Session: Canadian Cancer Society Lectureship: Recent Advances in Cancer Research —Dr. R. W. Begg, University of Saskatchewan; Leucémie – Dr. Claude P. Gendron, Montreal; Cancer Registration Scheme in Scotland – Prof. Thomas Anderson; Common Skin Malignancies – Dr. Donald Williams, Vancouver.

Afternoon: Annual General Meeting of the College of General Practice of Canada.

Evening: Dinner and Entertainment.

Wednesday, March 29

Morning: Medicine for Today Lectureship: The Fat and the Thin—Dr. T. M. Greenaway, Sydney, Australia; Histoplasmosis in Southwestern Ontario —Dr. E. L. Brown, St. Thomas, Ont.; Gastroenterology—Dr. Howard Weaver, Vancouver; Sodium and Water Needs of Patients – Dr. B. Scribner, University of Washington.

12.30 p.m. – Luncheon. Address: Dr. R. M. Parsons, President of the Canadian Medical Association.

Afternoon Session: Symposium on Functional Dyspepsia—Dr. T. M. Greenaway, Dr. C. R. Boileau and Dr. H. Weaver; Maladie de la vésicule biliaire —Dr. C. R. Boileau, Edmonton. Significance of the General Practitioner—Dr. J. H. McCreary, Dean of Medicine, University of British Columbia.

Evening: Annual Dinner and Dance.

Thursday, March 30

Morning: Medicine for Today Lectureship: Hypercholesterolemia—Dr. T. M. Greenaway; Acute Coronary Occlusion: Diagnosis and Treatment—Dr. Donald Munroe, Vancouver; Obesity in Children—Dr. Ben Shurman, Vancouver; Anemia Simplified—Dr. D. M. Whitelaw, Vancouver.

Afternoon Session: Symposium on Fertility—Dr. F. S. Hobbs, Dr. J. A. Hopkins, Dr. H. W. McIntosh and Dr. A. W. Wallace; Difformités du pied—Dr. Gordon Grant, Victoria, B.C.; Environment for Living—Mr. W. G. Leithead, Past President, Architectural Institute of British Columbia.

Features of the Scientific Assembly will include a full daily program of medical films; bilingual translation of all program sessions; more than 100 technical and scientific exhibits; a ladies' program; and the President's reception on Sunday evening, March 26.

Housing applications should be addressed to: Dr. D. M. King, 1807 West 10th Avenue, Vancouver, B.C.

OBITUARIES

DR. LESTER BREHAUT, aged 84, of Murray River, P.E.I., died December 4. A graduate of Dalhousie University, he practised in Murray River from 1903 until shortly before his death. He will long be remembered as the kindly physician who patiently answered calls, day or night, in fine weather or in storm, all over Southern Kings and Queens Counties. In recent years he frequently attended the grandchildren or great-grandchildren of earlier patients. The only period his practice was interrupted was two years ago when he suffered a broken hip in a fall on ice. He never refused a call, and horse and sleigh trips of 10 to 15 miles were a common occurrence.

Dr. Brehaut is survived by his widow.

DR. JOHN AINLEY BUTLER, aged 85, died December 10 in Bowmanville Memorial Hospital. A graduate of the University of Toronto in 1897, he practised in Baden and Newcastle, Ont.

DR. GRATTAN C. GRAHAM, aged 78, died November 13 at his home in Fenelon Falls, Ont. A graduate of the University of Toronto in 1913, he joined practice with his father in Fenelon Falls. He served as a medical officer in the R.A.M.C. during World War I.

Dr. Graham is survived by his widow and three sons.

DR. WILLIAM V. HARCOURT, aged 83, died November 21, at his home in Guelph, Ont. After graduating from the University of Western Ontario in 1910, he practised in Guelph until his death.

Surviving Dr. Harcourt are his widow and three sons.

DR. MOISE WILLIAM LEBEL, aged 69, died November 12 in Ottawa. A graduate of McGill University in 1919 and a member of the C.A.M.C., he was for some years superintendent of St. Vincent Hospital, Montreal, and Professor of Biology at Ottawa University.

Surviving Dr. LeBel are his widow, four sons and four daughters.

DR. ALBERIC MARIN, aged 67, died December 18 in Montreal. A graduate of Laval University and l'Hôpital St-Louis in Paris, Dr. Marin was a well-known skin specialist in Montreal and one of the founders of the Montreal Dermatological Society, of which he was president. He also served on the staff of the University of Montreal as professor of medicine.

Dr. Marin served with distinction in the Canadian Army during the First World War. He won the Military Cross and bar and was made a knight of France's Legion of Honor for an unusual action that earned him the name "The Fighting Doc of the 22nd". He was a captain and medical officer with the Royal 22nd Regiment at the battle of Cherisy, in which the regiment was decimated. He took command after all other officers had fallen and only 70 uninjured men could answer the roll call. The regiment held its position.

Surviving are his widow, a son and a daughter.

DR. J. HOWARD MUNRO, aged 79, died November 5 at his home in Maxville, Ont. He was the son of Dr. James T. Munro and together they served the community for almost 100 years. After graduating from McGill University in 1903, he did postgraduate work at the University of Edinburgh. He served during World War I as a medical officer in the Canadian Army and later with the French Army and was awarded the Croix de Guerre.

Dr. Munro is survived by his widow.

DR. JAMES T. THOMAS, aged 81, died on November 20 in Toronto General Hospital. A graduate of the University of Toronto in 1910, he practised in Caledon, Ont., for 48 years, until one month before his death. He used snowshoes, tractor, boat, and a horse and buggy to reach his patients. Known in the community as "Uncle Jimmy", he was honoured in 1949 by having a holiday proclaimed in his honour.

Dr. Thomas is survived by his daughter.

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PUBLIC HEALTH

SURVEILLANCE REPORTS OF EPIDEMIC OR UNUSUAL COMMUNICABLE DISEASES

Paralytic Poliomyelitis

Canada

During the four-week period from November 12 to December 10, 1960, a total of 61 cases of paralytic poliomyelitis were reported to the Epidemiology Division. The figure for the previous four-week period, from October 15 to November 12, was 106. The cumulative total for 1960 now stands at 809 cases.

To date, preliminary individual case reports have been received for 710 paralytic poliomyelitis cases, 87.7% of the 809 cases reported to December 10, and 63 deaths, 86.3% of the 73 deaths reported to December 10.

Paralytic Poliomyelitis Cases Distribution by Age Group and Vaccination Status (Preliminary Reports to December 10, 1960)

	Vaccination Status						
Age groups	*0*	*1*	*2*	*3+*	*N/K*	*Total*	*Per cent cases*
0 - 4	158	26	21	55	20	280	39.5
5 - 9	76	6	15	64	19	180	25.4
10 - 19	53	5	3	34	10	105	14.8
20+	108	7	10	15	4	144	20.3
N/K	—	—	—	—	1	1	
Total	395	44	49	168	54	710	100.0
Per cent doses	60.2	6.7	7.5	25.6	—	100.0	

Paralytic Poliomyelitis Deaths Distribution by Age Group and Vaccination Status (Preliminary Reports to December 10, 1960)

	Vaccination Status					
Age groups	*0*	*1*	*2*	*3+*	*N/K*	*Total*
0 - 4	13	—	3	5	—	21
5 - 9	1	—	—	4	1	6
10 - 19	10	—	1	—	1	12
20+	22	1	—	1	—	24
Total	46	1	4	10	2	63
Per cent doses	75.4	1.6	6.5	16.4	—	100.0

Infectious Hepatitis

In Nova Scotia, cases of infectious hepatitis have been reported from Moser's River in the Atlantic Health Unit (15) and from New Waterford in the Cape Breton North Health Unit (16).

The outbreak of infectious hepatitis previously reported at the R.C. Hostel at Inuvik, N.W.T., has now involved a total of 17 persons, and one case has been reported at the R.C.M.P. Gamma globulin has been given to all contacts.

Eight cases of infectious hepatitis have been reported from the R.C.A.F. Stations, Penhold and West Park, Red Deer, Alberta. In one family, the patient's wife has had the disease recently and the patient received gamma globulin about two weeks ago. In another family, the six children and the wife of the patient were given gamma globulin.

Influenza

About 200 cases of influenza were reported during November and December from various health units in Nova Scotia.

Tularemia

Two cases of tularemia have been reported from Calmar, Alberta, in women aged 46 and 70 years.

Whooping Cough

An outbreak of whooping cough has been reported from Manning and North Star, Alberta. Forty per cent of preschool and school age groups up to 10 years of age are affected. Manning, with a population of 900, is the most northerly town in the province and North Star is a hamlet about 12 miles from Manning. Many cases have occurred among immunized children and the course of the disease in these cases has been milder.

About 60 cases of whooping cough have been reported from Mission City, British Columbia, and the surrounding area. A large percentage of those affected were immunized in infancy.

From the Restigouche Health Unit in Bonaventure County, Que., several cases of whooping cough were reported during the month of November. The distribution by age group was as follows: 1 to 4 years, 5 cases; 5 to 9 years, 9 cases; 10 to 14 years, 12 cases; 20 to 29 years, 2 cases.

Dysentery

Five cases of dysentery due to *Shigella flexneri* have been reported from the Joseph Bighead Reserve at Goodsoil, Saskatchewan. The death, previously reported as due to shigellosis, was due to another cause.

D. KUBRYK, M.D., D.P.H., Chief, Epidemiology Division, Department of National Health and Welfare.

Ottawa, December 17, 1960

Paralytic Poliomyelitis Cases and Deaths Distribution by Age Group and Province (Preliminary Reports to December 10, 1960)

	Total		*0 - 4*		*5 - 9*		*10 - 19*		*20+*		*N/K*	
Province	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*
Newfoundland	46	3	33	3	8	—	3	—	2	—	—	—
Prince Edward Island	1	—	—	—	—	—	1	—	—	—	—	—
Nova Scotia	6	—	1	—	2	—	1	—	2	—	—	—
New Brunswick	39	2	13	—	15	1	9	1	2	—	—	—
Quebec	229	29	96	10	60	2	43	8	30	9	—	—
Ontario	39	2	16	—	12	—	5	—	6	2	—	—
Manitoba	12	1	5	—	5	—	1	—	1	1	—	—
Saskatchewan	50	7	18	3	15	2	9	1	8	1	—	—
Alberta	141	9	62	3	37	—	12	1	29	5	1	—
British Columbia	146	10	36	2	25	1	21	1	64	6	—	—
Yukon	—	—	—	—	—	—	—	—	—	—	—	—
Northwest Territories	1	—	—	—	1	—	—	—	—	—	—	—
Total cases and deaths	710	63	280	21	180	6	105	12	144	24	1	—
Case fatality rate %	8.9		7.5		3.3		11.4		16.7		—	

BOOK REVIEWS

THE TORCH. Wilder Penfield. 367 pp. Illust. Little, Brown & Company (Canada) Limited, Toronto, 1960. $5.00.

Not much is known with certainty about Hippocrates. Thus to make him the central figure in a historical reconstruction calls for an extensive and accurate knowledge of Greek history and a facility of invention in the matter of suitability of characters and the probability of described events. In this work, there is evidence of enough painstaking and prolonged probing of history to give a verisimilitude which is convincing even to the sharper critics.

The author of this book has made a laudable effort to picture Hippocrates as a real, sentient practitioner of medicine who carried on the management of disease in the established methods of Greek medicine of that day. To illustrate some of the difficulties met with by Hippocrates and his approach to their solution, there are descriptions of such pathological conditions as epilepsy, pneumonia, fractures, phlebitis, inanition and pulmonary embolism. In the presence of these lesions, Hippocrates exhibits a serenity and a sureness that some of our modern physicians might envy. He also puts forward theories and suggestions that are not unlike those we hold today. These are not anachronistic lapses on the part of the author, for the actual historical errors are few and none is serious.

The book is decidedly worth-while but unfortunately the circle of its readers will not be large. It is a lamentable fact that the number of those who are interested in the story of medicine is dwindling year by year. To those who like to browse in the field of history this book can be wholeheartedly recommended.

CARCINOMA IN SITU OF THE UTERINE CERVIX. A Study of 235 Cases from the Free Hospital for Women. Gilbert H. Friedell, Arthur T. Hertig and Paul A. Younge. 150 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $8.25.

This small volume is not a comprehensive text on the subject, but is a monograph which provides a detailed review of 235 cases seen at the Free Hospital for Women in Brookline, Massachusetts, between 1926 and 1952. An introductory chapter provides an interesting historical summary of the contributions of early workers in the gradual identification of the entity of carcinoma *in situ* of the cervix. The bulk of the volume deals with an analysis of the authors' cases from histological, clinical and therapeutic viewpoints. Many controversial issues, such as the criteria for diagnosis, the significance of gland invasion, and the merits of punch biopsy versus cone biopsy in diagnosis, are considered and the authors' views expressed. The results of therapy are provided, demonstrating a marked lack of uniformity in the management of cases that were treated in an era when the ideal treatment of this lesion was even less clear than it is today.

This is a monograph for the pathologist and the gynecologist who are serious students of this disease, rather than for the general reader. The detailed description of cases, the numerous photomicrographs of high quality and the authoritative opinions of the authors make this a valuable contribution to the literature concerning this interesting disease.

ATLAS OF TUMOR PATHOLOGY, SECTION IV, FASCICLE 10A, TUMORS OF THE ODONTOGENIC APPARATUS AND JAWS. Joseph L. Bernier. 107 pp. Illust. Armed Forces Institute of Pathology, Washington, D.C., 1960. $1.00.

Over the years a great contribution to oncology, particularly in the field of pathology, has been made by the publication of the various atlases of tumour pathology by the Armed Forces Institute of Pathology, Washington.

This atlas on tumours of the odontogenic apparatus presents, in a short space of 107 pages, a clear, succinct account of tumours of the hard and soft tissues of the mouth.

After reviewing briefly the anatomy of the jaws and development of the teeth, the author proceeds to an orderly description of cysts and benign and malignant tumours of the jaws and teeth. The classification of the lesions and the synonyms are helpful. The descriptions are clear. The illustrations are superb and readily understood. In order to avoid overlapping with some of the material in other fascicles past and future, a few gaps are evident. For example, under "tongue", no mention is made of carcinoma or of myoblastoma.

This atlas fulfils a distinct need for the information it provides. It should be of great value to all pathologists as well as to oral and dental surgeons.

EPIDEMIOLOGIC METHODS. Brian MacMahon, Thomas F. Pugh and Johannes Ipsen. 302 pp. Illust. J. B. Lippincott Company, Philadelphia and Montreal, 1960. $7.50.

Epidemiology is no longer limited to the study of infectious diseases but has been broadened to include investigation of noninfectious diseases, arteriosclerotic heart disease, cancer, accidents, and mental disorders. This broadening process has necessitated some modification of methods, though not necessarily of principles. This text outlines the "methods", the "how" and the "why", such as the significance of age, sex, ethnic group, place, time, birth order, and parental age. The "double blind" experiment so commonly used in assessing the value of therapeutic agents in clinical medicine is discussed.

Epidemiology is no longer confined to the practice of public health but is a discipline to be employed in clinical medicine as well. This book should find a wide field of interest as the science of medicine requires an epidemiological approach.

HANDCRAFTS FOR THE HOMEBOUND HANDICAPPED. Mildred Kroll Rich, Teacher of Handcrafts for Homebound Children, Bureau for the Education of the Physically Handicapped, Board of Education, City of New York. 102 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $6.00.

The title of this book is misleading in that, as stated in the preface, it is intended as a guide to handcrafts for children.

Some of the activities outlined could scarcely be described as crafts but rather as time-occupying hobbies. In fact, apart from their diversionary value they would have limited use in treatment of the organically disabled patient, e.g. with rheumatic or neurological disorders.

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EYE SIGNS IN GENERAL DISEASE. F. Herbert Haessler. 113 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $6.25.

This book, by Dr. Herbert Haessler of Wisconsin, is a brief, accurate and well-organized description of both common and many unusual abnormal ocular findings, and their clinical significance in systemic disease.

The book is well written and easily read. Its brevity and lack of illustrations are compensated for by the excellent index and bibliography, and its relative inexpensiveness.

The outline follows the anatomical structures seen during the course of a physical examination. Hence the book is of extreme value to the general physician and specialist in internal medicine, as well as to the student preparing himself for examinations. Because of lack of details in the descriptions, this book is of less value to the ophthalmologist. No attempt is made to discuss prognosis or treatment of the general diseases mentioned.

The author correctly reminds the physician that he will find more abnormalities if he understands them and looks for them.

KLINISCHE NEURORADIOLOGIE (Clinical Neuroradiology). Edited by Kurt Decker, München. 507 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1960. $54.75.

This is a very elaborate study of clinical neuroradiology by the best-known authors in this very interesting field. There are 29 known books or chapters in standard textbooks on diagnostic radiology in English, French, German, Italian and Czech which are listed by the authors. Among the better-known texts in the English language are those by Pendegrass *et al.* and by Orly, as well as the Swedish publications. In addition, valuable material has been contained in the symposia neuroradiologica.

The textbook under review contains 14 chapters. The first chapter by Fischgold and Metzger from Paris deals with the methods used in plane radiography of the skull and with demonstration of the role of tomography in the diagnostic radiology of the skull, a subject in which Fischgold excels. In the second chapter, Decker describes the various techniques in which contrast media are used, such as cerebral and vertebral angiography and pneumography and their application in various conditions. In other chapters, Decker discusses contrast and air myelography, the investigation of skull injuries and their sequelae, diseases of the cerebral vasculature, manifestations of cerebral thrombosis, angiographic manifestations of brain infarcts and aneurysms, arteriovenous fistulae and cerebral hemorrhage.

Dr. D. L. McRae from the Montreal Neurological Institute has written a chapter on neuroradiology of the patient with epileptic seizure and its relation to the growth of the skull. McRae also discusses the investigation of atrophy and hypertrophy of the brain and, in another chapter, deals with the problem of degenerative disc disease of the spine. Dr. McRae has devoted many years of study and research to these subjects and is internationally known for his many contributions to the radiological literature.

A large section of the textbook is devoted to Decker's chapter on space-occupying lesions of the skull with detailed description of the methods used in their diagnosis. Pediatric neuroradiology is dealt with by Taveras from the Neurological Institute in New York. The neuroradiological procedures in psychiatric conditions such as those associated with brain atrophy, some psychoses, syphilis and other disorders are reported by Decker. Schunk and Mark from Boston describe the radiological procedures used in stereotactic operations.

This textbook fills a gap in the radiological literature. All its chapters are well written and the editor has contributed greatly to the lucidity of the text. The abundance of excellent illustrations and their legends make it a valuable reference book. We would recommend that it be translated into English and thus be made available to a large group of men interested in the radiological diagnosis of the central nervous system.

The publishers are to be congratulated on the generous size of the illustrative material and the graphic qualities of this book.

THE SURGEON'S GLOVE. Justine Randers-Pehrson. 95 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $5.00.

This is a short review by a non-medical writer of the brief history of the glove in surgery. There is a good bibliography, and the account contains some interesting anecdotes of the attitudes of the great surgeons of the time (1890-1910) when the subject was so controversial. One cannot help but feel that the wide adoption of gloves awaited not so much the conviction of surgeons of their merit but the development of rubber processing to the point where a glove could be made which was not a mechanical monstrosity. Indeed the year of development (1878) of such a satisfactory process was the same as that of Koch's paper on wound sepsis.

The popular style of writing and non-medical viewpoint detract from the value of an otherwise interesting monograph. For example, on page 25 appears this remarkable statement: "This was the heyday of disinfection. Every surgeon worth his salt burst into print with his own infallible formula for hand cleansing."

THE CELL NUCLEUS. Proceedings of an informal meeting held at the Department of Radiotherapeutics, University of Cambridge, August 31 and September 1, 1959, by the Faraday Society. Chairman, J. S. Mitchell. Butterworth & Co. (Publishers) Ltd., London; Butterworth & Co. (Canada) Ltd., Toronto, 1960. $11.00.

During the past century cellular physiology and pathology have given a new concept and impetus to all biological sciences. It might be predicted that the coming century will centre its interest about the nucleus. The volume under review is dedicated to this subject.

The book is divided into five broad subject groups: "Functions of the nucleolus", "Synthesis of deoxyribonucleoprotein in the cell", "Nuclear enzymes" and "The structure of deoxyribonucleoprotein in solution and in the nucleus".

This book, written by a large number of contributors, presents in one volume a summary of present-day knowledge of the cell nucleus. Novel points and freshly developed techniques have led to a shift in focus allowing for new stock-taking. This is precisely what the book offers to its reader. To all of those in the various branches of biological science who have preserved the desire to remain informed, to broaden, reorient and reaffirm their basic knowledge, the book will be most valuable.

SEA WITHIN. The Story of Our Body Fluid. William D. Snively, Jr. 143 pp. Illust. J. R. Lippincott Company, Montreal, 1960. $3.95.

In his preface, the author states that "this book is intended primarily for the great number of laymen who are intrigued by the 'scientific aspects of human life'," and he adds that "it may also be of interest to physicians, nurses, technicians, dietitians, and students as background reading for technical treatises on body fluid."

The reviewer has had very little experience with laymen intrigued by the scientific aspects of human life, and he cannot predict whether or not they will enjoy this book. His impression is that they will find it heavy going. This is not to say that the author has not done extremely well. He is obviously competent in the field and he expresses himself clearly and accurately. However, there is perhaps no field in medicine more difficult to teach and to comprehend than water and electrolyte metabolism. One cannot help but feel that in choosing this as the subject of a work for laymen, Dr. Snively has taken on an almost impossible task. All one can do is wish him luck and express the hope that sales to the reading public will reach or exceed his expectations.

The reviewer agrees with the author that the book may be of interest to nurses, technicians and dietitians. To these one would add teachers of biology in high schools. Its interest or usefulness for physicians and medical students is uncertain. There is already an abundance of texts and monographs to meet the needs of medical graduates and undergraduates. For them there is no easy road to the detailed understanding of water and electrolytes which they must have, and it is doubtful if Dr. Snively's book will help them.

DAS HIRNGESCHADIGTE KIND (THE CHILD WITH BRAIN DAMAGE). Karl-Hermann Wewetzer. 117 pp. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1960.

The title of this volume is somewhat misleading, for it is not a book on the etiology, diagnosis and management of cerebral damage in the child, as one might expect. It is an account of a series of tests on two groups of children designed to prove the postulate that brain damage does not result in a disturbance of isolated functions, but rather in a change of the entire psychological structure and the personality as a whole.

Forty-two children who had suffered cerebral damage from birth trauma, encephalitis, meningitis, neoplasm or various other causes were subjected to 10 psychological tests. Their ages ranged from 6 to 16 years, and their I.Q. from 65 to 135. The control group also comprised 42 children of the same age group and a similar I.Q. who had no known brain damage. Most of the tests are described in detail, and their results are analyzed carefully. The object of this study was to detect deficiencies characteristic of the children with "exogenous" brain damage as opposed to those whose low I.Q. was "endogenous" or familial. The differences in the performance of the two groups were apparent and statistically significant.

The book is of interest to child psychologists and psychiatrists. It requires a thorough knowledge of the German language and the special terminology.

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THE MURDEROUS TRAIL OF CHARLES STARKWEATHER. James Melvin Reinhardt. The Police Science Series. Edited by V. A. Leonard. 147 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $6.25.

Mass murder always has some special fascination. When a 19-year-old lad accompanied by a 14-year-old girl-friend kill 11 people, ten of them within a week, such a crime surely deserves to be included in any police science series. The peculiarities of teen-age crime, the special features of mass murder, the difficulties of detecting the unknown amateur without previous conviction, the still vexed question of criminal responsibility, and especially on this continent the influence of easily bought firearms and the automobile, are all worth attention.

One would expect in a Police Science Series that the description, detection, explanation, and prevention of such crimes would be foremost, while medico-legal and psychosocial issues should simply be in the background. The reviewer started this book hoping to learn something of a police scientist's point of view, but Professor Reinhardt has adopted what is a puzzling approach and one which must be almost incomprehensible to many of his policemen readers. If one has understood him correctly, he has attempted to give a picture of Charles Starkweather's world by means of extensive quotations from 30 hours of interviewing supplemented by excerpts from the mass murderer's own writings. In the hands of a very skilled novelist whose technique is impeccable this allusive and indirect method may have something to commend it. Unfortunately Professor Reinhardt is no novelist. His book is muddled and badly planned and in spite of the inherent interest of the subject, difficult to follow. Having no personal experience with police work, the reviewer can only hope that those who have, learned something from it.

Apart from a few lines stating that the psychiatrists for the defence and prosecution disagreed, Starkweather's mental state receives little direct discussion. His holocaust of killing is ascribed to an ingrown and gnawing hatred which the author describes in tedious and repetitive detail. From pages and pages of direct and indirect quotations it seems likely that the boy suffered from a moderately severe paranoid schizophrenia with clearly described disturbances in perception, affect and thinking. For some reason the author ascribes much of this to what he calls fantasy, a term as vague as it is misleading and one which he does not try to define.

Doctors and policemen both need to know more about recognizing those few schizophrenic people who are a grave danger to others and distinguishing them from the great majority who do not harm anyone, but nothing is said of this.

The author also neglects what seemed to your reviewer to be something that should be drawn to the attention of both police and public. This is that in countries which are lax in controlling firearms and automobiles, explosions of this sort are far more likely to occur and far more difficult to detect.

MEDICAL NEWS *in Brief*

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THE PREVALENCE OF TUBERCULOSIS AMONG PHYSICIANS

Tuberculosis, which in the past has frequently been considered an occupational disease among doctors because of their exposure to undetected cases during medical student days and on the hospital ward, is declining as a risk among physicians in the United States.

Evidence of the decline was revealed in data obtained from a tuberculin-testing program at the Johns Hopkins School of Hygiene and Public Health, reported by P. E. Sartwell in the notes section of the November 1960 issue of *the American Review of Respiratory Diseases.*

Over a nine-year period, 279 physicians were tested; 137 of these were from the United States and 142 from other countries. Of the United States residents, 47% were tuberculin reactors while 81% of those from other countries were reactors. The percentage of reactors ranged from 32% among the United States physicians in the age group 25 to 29 years to 78% among those 40 years of age and older.

The sharp rise in percentage of reactors more than 40 years old among American physicians is thought to reflect not only an age effect but also the greater opportunity for infection that existed in earlier years. Thus, physicians tested at age 50 were exposed, before entering medical school, to the risks which prevailed from about 1910 to 1930 and to occupational risks from about 1930 onward. There is much evidence that the prevalence of open, and especially undetected, tuberculosis as encountered in hospitals, clinics, and practice is declining.

Whether medical students should be vaccinated with BCG is debatable, but the opinion was expressed that vaccination of medical students in the United States is still advantageous, although in a relatively short period of time the risk may be so low as to warrant discontinuation of vaccination, especially if periodic tuberculin testing is substituted. The hazard for practitioners in some other countries appears still to be large.

DOCTORS GIVE FREELY

A remarkable set of facts on the amount of medical care physicians give without compensation has been uncovered by *New Medica Materia* in a recent study based on a nationwide sampling of private practitioners.

"That physicians have always given freely of themselves is no longer newsworthy," the monthly medical magazine noted editorially. "People have come to expect the physician to be possessed, in larger measure than most, with the instinct of humanity. But that the free medical care donated by all private practitioners in the U.S. now totals a gargantuan $658 million a year is a fact which is bound to give pause—much pause."

The survey disclosed that more than 98% of all physicians give free medical care and that 60% of all doctors devote 10% or more of

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no chelators
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in rapidly disintegrating tablets for ready availability and a *full measure* of therapeutic effectiveness

P.G.A. 0.25 Each tablet contains Penicillin G Ammonium (444,250 i.u.) equivalent to 0.25 Gm. free Penicillin G. In bottles of 12 and 100 tablets.

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DOSAGE The majority of commonly-encountered infections caused by penicillin-sensitive organisms can be conveniently treated by the administration of 0.5 Gm. P.G.A. twice daily or 0.25 Gm. P.G.A. three times daily. For infants and children, one-half to one teaspoonful of P.G.A*tric* three times daily. As is true of most medication, absorption is maximal when the stomach is empty.

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MEDICAL NEWS *in brief*

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their working hours to such work. Specialists donate $381 million, an average of $4812 each; general practitioners give $277 million, an average of $3360. Total value of free care given by doctors has gone up 10.6% in five years. The breakdown of where the free care goes is as follows: private patients treated without charge, 39.9%; outpatient clinic service, 22.7%; hospital ward service, 26.5%; students, campers, Scouts, amateur athletes, blood donors, doctors' kin, clergymen, emergency, and charity patients, 10.9%. Another interesting fact is that the $658 million annual contribution by physicians is so great that it even exceeds the federal-state program of medical care for the elderly recently legislated by the U.S. Congress. Total cost of the new program is expected to be $263 million for the first year and $520 million for each year thereafter. — *A.M.A. News*, November 28, 1960.

NEWS FROM W.M.A.

Dr. Louis H. Bauer, Secretary General of the World Medical Association since 1948, became Consultant to that organization on January 1, 1961. Dr. Bauer has been closely associated with organized medicine since 1929. He is a past president of the American Medical Association, the Aeromedical Association (now, Aerospace Medical Association), the Nassau County Medical Society, and the Medical Society of the State of New York. He is a consultant cardiologist to five hospitals in Nassau County, New York; Consultant and Former Chairman of the Board of Directors, United Medical Service (New York's Blue Shield Plan); and a member of the New York State Public Health Council. He received an honorary degree of Doctor of Science from the University of Sydney (Australia); was the recipient of the Joseph Bancroft Medal (Queensland, Australia); and was awarded the Honorary Gold Key, Medical Faculty, University of Vienna, in 1955. He is an Honorary Flight Surgeon of the French Air Force and recently received the Paracelsus Medal, highest honour awarded by the German Medical Association (Deutsche Aerztetag).

Dr. Heinz Lord of Barnesville, Ohio, succeeds Dr. Bauer as Secretary General of the World Medical Association.

The XVth General Assembly of the World Medical Association will be held in Rio de Janeiro, Brazil, September 15-20, 1961.

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EXPANSION IN ONTARIO'S MENTAL HEALTH FACILITIES

Dr. M. B. Dymond, Ontario Minister of Health, speaking on the occasion of the recent opening of a new 6½ - million - dollar mental health treatment unit at the Ontario Hospital, Hamilton, announced his department's plans for further extensive developments in the mental health field. In the past two years the provincial health department has established a psychiatric institute for children, the first of its kind in Canada, in buildings previously operated as a tuberculosis sanatorium in London, Ontario. Another

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former sanatorium at Gravenhurst has been converted to a hospital-school for retarded children, housing 300 patients. The cornerstone of a new hospital-school in southwestern Ontario has been laid and the hospital will be in operation within a year. Two more hospital-schools are in the planning stage, as are a psychiatric institute and another 600-bed hospital for the mentally ill. In addition the contract for the first of three infirmaries has just been let. These infirmaries will provide a new type of accommodation in the form of home-type setting for the aged and chronic mentally ill, those who cannot profit by further active treatment and for whom the family or community cannot or will not provide. At present it is estimated that there are about 8000 such persons in Ontario mental hospitals. Provision of the infirmary type of accommodation will permit the hospitals to concentrate upon their primary function, which is the active treatment of the acutely ill, with a view to restoring them as quickly as possible to the flow of normal society.

Dr. Dymond commented further on the exciting and important new trails being explored in the area of treatment of mental illness with the aid of the most modern facilities available.—*Résumé*, Canadian Mental Health Association, November 1960.

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INTERNATIONAL CONFERENCE ON AMINE BUFFERS

A three-day conference of scientists representing a number of areas of research was held by the New York Academy of Sciences on December 12, 13 and 14. The subject of the conference was "*In vitro* and *in vivo* Effects of Amine Buffers". Chemists, physicians, and biologists read a total of 40 papers covering research on various aspects of laboratory and hospital studies. Scientists from Sweden, Denmark and France participated, as well as others from the USAF Aerospace Medical Center in Texas, the Naval Research Laboratory in New London, Conn., the Army Institute of Research and the National Bureau of Standards, in Washington, D.C.

Buffering controls acidity and alkalinity, hydrogen-ion and salt concentrations, and other factors which, in turn, determine the ability of organisms, including man, to survive. In submarines, for example, carbon dioxide concentration in the blood is a constant hazard, and buffers are employed to absorb the gas. Other amines can control the plasma protein binding activity of thyroid hormones, the activity of enzymes, and the permeability of tissues.

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AMERICAN COLLEGE OF SURGEONS 1961 SECTIONAL MEETING IN WINNIPEG

The American College of Surgeons will hold the last of its four 1961 Sectional Meetings in Winnipeg, Manitoba, from April 6 to April 8. All members of the medical profession are invited to attend this Canadian meeting. Headquarters will be the Fort Garry Hotel.

Dr. Kenneth R. Trueman, Assistant Professor of Surgery, University of Manitoba, is chairman of the Advisory Committee on Local Arrangements. He and his committee have planned a program encompassing a broad field of interest to general surgeons and surgical specialists. Assisting Dr. Trueman are the following Canadian Fellows of the College: Albert C. Abbott, Elinor F. E. Black, Cecil William Clark, Morley Cohen, Colin C. Ferguson, Howard N. Reed, James W. R. Rennie, George H. Ryan, Otto A. Schmidt and P. H. T. Thorlakson.

The opening session on Thursday, April 6, will be presided over by Dr. Trueman, and will be one of three "How I Do It" clinics to be held during the meeting. These clinics are educational demonstrations which have proved extremely popular at other Sectional Meetings. Panel discussions, symposia, medical motion pictures, and scientific papers in general surgery and various surgical specialties will comprise the rest of the program.

The closing session on Saturday afternoon will be a symposium on "What's New In Surgery," moderated by Dr. Colin C. Ferguson, Chairman of the Department of Surgery, University of Manitoba.

Additional information concerning the program and registration may be obtained by writing to Wm. E. Adams, M.D., Secretary, American College of Surgeons, 40 East Erie St., Chicago 11, Illinois.

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The Canadian Medical Protective Association

PRESIDENT – GEORGE W. ARMSTRONG, M.D.

A mutual medical defence union founded in 1901, Incorporated by act of Dominion Parliament, February, 1913, and affiliated with the Canadian Medical Association, 1924.

Assistance offered by the Association may include:

(1) Advice about the best way to avoid suit when threats have been made.

(2) The actual defence of the suit and the payment of costs thereof.

(3) The payment of damages should they be assessed.

Address All Correspondence to the Secretary-Treasurer,

26 Nepean St., Suite 115, Ottawa 4, Canada

APPLICATION FOR MEMBERSHIP

I, ...
Please print name in full

date of birth....., a qualified medical practitioner, hereby apply to be enrolled as a member of the Canadian Medical Protective Association.

Graduate of..... University, year..... ...;

a duly licensed practitioner of the Province of.....

since the year.....; a member in good standing of

..... Medical Association.
Canadian or Provincial

Type of practice: General ☐ Specialist ☐

Specialty .....

Certified?.....

Have you had threats or legal action against you?
Yes ☐ No ☐

If accepted I agree to abide by the rules and regulations of the Association.

Date..... Signature.....

Office Address .....
Street name and number—NOT name of building

.....

If a member of the Canadian Medical Association or Provincial Division thereof no further recommendation is required. If not, recommendation by two members of the Canadian Medical Protective Association is necessary.

1. .....
Please print name beside signature

2. .....

Annual Fee twenty dollars, half rates from July. If cheques used for remittance, have marked payable at par, Ottawa, or add fifteen cents to cover cost of collection.

MEDICAL NEWS *in brief*

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THIRD WORLD CONGRESS OF PSYCHIATRY

The Third World Congress of Psychiatry will be held June 4-10, 1961, in Montreal, under the auspices of the Canadian Psychiatric Association and McGill University.

Meeting for the first time on the American continent, the congress is expected to attract some 3000 delegates from 62 nations. Representatives will come from psychiatry and such allied fields as general medical practice, psychology, biochemistry, nursing, sociology, anthropology, social work and pharmacology. In place of a single theme, the organizing committee has grouped all scientific presentations into a number of functional approaches as desired by the majority of the members. Thus, under the general headings, phenomenological or observational, experimental including therapeutic, and interpretive or theoretical, practically every area of special interest in psychiatry will be examined at the congress. There will be simultaneous translations into English, French, German and Spanish of all plenary sessions and many of the other major meetings.

Information about the meeting may be obtained from the General Secretary, III World Congress of Psychiatry, 1025 Pine Ave. West, Montreal 2, Quebec.

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VOCATIONAL REHABILITATION OF PSYCHIATRIC PATIENTS IN THE U.S. VETERANS ADMINISTRATION

Major advances are being made in reducing re-hospitalization rates of U.S. Veterans Administration psychiatric patients, through co-operation of hospitals and community vocational and employment services. VA hospitals where patients receive these intensive preparatory and follow-up services have reported readmission rates as low as 12%, as compared with the 50% rate for mental hospitals in the United States generally. Many more VA hospitals are organizing such programs.

VA hospital services to prepare psychiatric patients for employment include an industrial therapy program, in which patients work at part-time, unpaid hospital jobs; a night hospital program, in which patients work or train in the community during the day and return to the hospital at night for treatment; a member-employee program, a family care program, and exit wards. In the member-employee program, the patient is released from patient status but is retained at the hospital as a full-time paid employee for up to one year, to rebuild or strengthen work skills and attitudes. In the family care program, patients are placed in selected homes to relearn social living skills, which often are essential to their later vocational adjustment. The exit wards offer concentrated therapeutic, social, and vocational services for patients nearing completion of their hospital stay.

These programs are supplemented by individual and group counselling by VA counselling psychologists and are geared to capitalize upon and extend hospital resources such as physical medicine

and rehabilitation, special services, and other physical, pharmacological, and psychological therapies.

Since one of the major contributing factors leading to the necessity of rehospitalization of previously treated psychiatric patients is the frustration that arises from inability to find and hold a suitable job, the VA also helps its patients secure employment on discharge from hospital, either directly or through referral to community agencies. The VA hospitals possess the advantage of having, in each state, the services of VA regional offices, which provide outpatient treatment, trial visit supervision, and support for vocational training. However, since few veterans are still eligible for or in need of the regional office resources, state agencies such as the U.S. Employment Service, the Division of Vocational Rehabilitation, and others are invited to collaborate with VA hospital personnel in helping the psychiatric patient with his vocational plans and post-hospital adjustment. At the national level, co-operative agreements have been developed between the VA, the Department of Labor, the Veterans Employment Service, and the Office of Vocational Rehabilitation. These formal agreements may be modified at the local level to outline more explicitly the activities of those concerned, define the nature of information to be included in referral, progress, and placement reports, and for similar purposes. VA hospital personnel provide social, psychological, and vocational assistance to former patients, usually through field trips by the social worker or counselling psychologist to the home community of the veteran.

VA counselling psychologists also maintain close liaison with personnel in community agencies such as the U.S. Employment Service and Division of Vocational Rehabilitation, with vocational training schools, and frequently with employers of former patients.

The Veterans Administration is now planning a national program of carefully controlled studies of hospital and community factors which best contribute to the vocational rehabilitation and employment of the mentally ill.

PROCEEDINGS OF THE THIRD CANADIAN CONFERENCE ON MENTAL RETARDATION

The *Proceedings of the Third Canadian Conference on Mental Retardation* have now been printed in a volume of 130 pages which is available for the sum of $1.00 from the Canadian Association for Retarded Children, 317 Avenue Road, Toronto 7.

This conference was held in Montreal, P.Q., on September 14, 15 and 16, 1960.

SOCIETY FOR THE ADVANCEMENT OF NEUROPSYCHOPHARMACOLOGY

The advancement of neuropsychopharmacology was the theme of a conference held in New York on November 12 and 13. Clinical psychiatrists, educators, and research workers in basic sciences as well as clinical investigators participated. The Chairman of the conference was Paul H. Hoch, M.D., Com-

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missioner, Department of Mental Hygiene, State of New York, and the Secretary *pro tempore* was Theodore Rothman, M.D., Department of Psychiatry, University of Southern California School of Medicine. Evaluations of present-day methods of training investigators and testing drugs, and the difficulties in obtaining swift dissemination of accurate information to the medical profession, were critically discussed.

Canadian participants in the conference were Dr. Abram Hoffer, Assistant Professor of Psychiatry, University of Saskatchewan, and Dr. Heinz E. Lehmann, Clinical Director, Verdun Protestant Hospital.

One of the recommendations was that a new society be formed, with the purpose of advancing knowledge in this important area of psychiatric research. An organizing committee appointed to implement these recommendations included Dr. Theodore Rothman as Chairman, with Dr. Paul Hoch, Dr. Jonathan O. Cole, Chief of Psychopharmacology Service, National Institutes of Health, Bethesda, Md.; Dr. Frank J. Ayd, Jr., Chief of Psychiatry, Franklin Square Hospital, Baltimore, Md.; and Dr. Paul Feldman, Director of Research and Professional Education, Topeka State Hospital, Topeka, Kansas. Dr. Bernard Brodie of the National Institutes of Health will serve as consultant in basic sciences.

The next meeting of the committee is scheduled for February 1961 and it is probable that the new society will be organized in time for the May meeting of the American Psychiatric Association.

GRANTS AVAILABLE FOR DEMOGRAPHIC STUDIES

The Population Council is offering 25 fellowships for training in the field of population at the predoctoral and postdoctoral levels during the 1961-62 academic year. These awards are available for study in appropriate universities in the United States and other countries.

Council fellowships are for training in demography, although related study in sociology, economics, biostatistics, and other relevant fields may form part of a total program. The plan of study and choice of university are made by the applicant. A candidate must have completed at least one year of graduate study.

Applications are accepted from well-qualified persons of all countries, preferably under 40. Particular consideration is given to students from the economically underdeveloped areas.

Fellows receive support for full-time study, usually for a period of 12 months. The basic stipend is $2700; this may be supplemented to provide for tuition, maintenance of dependents, travel and exceptional expenses. It may be diminished to take account of lesser needs or partial support from other sources. Somewhat larger stipends are granted to postdoctoral than to predoctoral fellows.

Applications for the academic year 1961-62 should be received before February 1, 1961. Requests for application forms should be addressed to: The Population Council, 230 Park Ave., New York 17, N.Y.